



# "Informed" Consent and Human Experimentation: Present Status, Pitfalls, and the Need for Reform

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Informed Consent and Human Experimentation: Present Status, Pitfalls, and the Need for Reform

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April 24, 2001

I didn't research it. But I shouldn't have to research it. I

believed these guys, everything they were telling me.<sup>1</sup>

The above statement of Paul Gelsinger, who withdrew his teenage son Jesse from life support after an infusion of gene-altered viruses meant to correct an enzyme deficiency triggered an immune reaction that went awry, expresses a parent's distress at being inadequately advised about a University of Pennsylvania gene therapy experiment in which he encouraged his child to participate. Neither father nor son recognized that the experiment bestowed no benefit upon the teenager and had been fashioned to evaluate the safety of a

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<sup>1</sup>Sheryl Gay Stolberg, *Teenager's Death is Shaking Up Field of Human Gene Therapy Experiments*, N.Y. TIMES, January 27, 2000, at A20.

treatment for babies with a fatal form of Jesse's disorder. Mr. Gelsinger, who now regards his decision to trust Penn researchers as naïve, was unaware both of the risks involved in the study and that despite three hundred clinical trials, gene therapy had never cured anyone.<sup>2</sup> Researchers instead procured Jesse's participation by implying that therapy received might combat his disease.

This case proves particularly troubling because of a flagrant disregard for the process of informed consent: federal regulations mandate that potential risks and benefits be outlined to patients in lay language and that if some participants in a study experience grave side effects, all volunteers must be apprised of developments and consent again. The informed consent form the Gelsingers reviewed, however, excluded mention of monkeys' death subsequent to administration of a similar treatment, and when patients suffered changes in liver enzyme levels dire enough to terminate the trial, the consent form remained unrevised. FDA investigations further reveal that researchers enrolled all eighteen patients without completing eligibility forms and poorly documented the consent process for half of these subjects. Such flaws in informed consent are routine; the director of the Office for Protection from Research Risks reports that over 90 percent of cases of alleged abuse he investigates uncover lapses in informed consent.<sup>3</sup> Exacerbating the distress this case evokes is the fact that the teenager was not seriously ill before his death. His mild liver disorder was controlled adequately through diet and medication. The incident thus highlights the manner in which optimism divaricates in clinical trials when researchers hope to discover if novel treatments prove hazardous, yet subjects expect a cure. Although the population at large generally looks favorably upon biomedical research, this botched gene therapy study provokes questions concerning the nature of medical progress, the procedures by which cutting-edge technology is and should be developed, executed, and evaluated, as well as what constitutes proof of therapeutic efficacy and who should render efficacy determinations.<sup>4</sup> Researchers' quests for general

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<sup>2</sup>See *id.*

<sup>3</sup>See *id.*

<sup>4</sup>See Nancy M.P. King and Gail Henderson, *Treatments of Last Resort: Informed Consent and the Diffusion of New*

progress or a cure now clearly endanger basic values such as human dignity and autonomy, leading Senator Bill Frist to comment after Congressional hearings on the Gelsinger tragedy that we must confront a multisystem failure of safeguards currently in place if we are to protect patients.<sup>5</sup> Pharmaceutical companies, researchers, advocacy organizations, and politicians have criticized human experimentation regulation, currently achieved through a crazy quilt of hortatory codes and maxims, scattered federal laws and regulations and... Institutional Review Boards (hereafter IRBs).<sup>6</sup> IRBs and regulations do not sufficiently entrench the rights of patient-subjects. While IRBs must exercise heightened vigilance to safeguard vulnerable populations such as prisoners, children, pregnant women, and the mentally disabled<sup>7</sup>- i.e. those particularly susceptible to exploitation and duress due to factors such as diminished decision-making abilities or captivity of institutionalization- federal regulations utterly fail to provide adequate protections for numerous groups, including the terminally ill, children, and the mentally disabled. Guidelines additionally have worked systematically to disadvantage other groups, most notably women. Traditional exclusion of females from research under protectionist auspices has led to the marketing of medical products posing danger to women and has deprived seriously ill women of access to experimental treatment offering their only hope of survival. Modern medical breakthroughs compound the shortcomings of the regulations, for the advent of AIDS and HIV treatments as well as experimental cancer therapies have rendered access to trials, rather than exclusion, the objective of vulnerable populations. Patients demanding easier access to new therapies willingly volunteer for unproven treatments. This creates difficulty in that patients cannot make informed choices to try potentially dangerous new technologies due to numerous unknowns involved<sup>8</sup> and underscores the bifur-

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*Technology*, 42 MERC. L. REV. 1007, 1009 (1991).

<sup>5</sup>See Sheryl Gay Stolberg, *Senators Press for Answers on Gene Trials*, N.Y. TIMES, February 3, 2000, at A25.

<sup>6</sup>Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 CATH. LAW. 455, 474 (1996).

<sup>7</sup>See 45 C.F.R. §46.111(a)(3) (1992).

<sup>8</sup>See King and Henderson, *supra* note 4, at 1008-09.

cation of patients' autonomy and their best interests. As human experimentation has come to be regarded as beneficial rather than suspect, the traditional line between research/experimentation and clinical practice/therapy has blurred and monetary issues have subordinated concerns for the rights and well-being of patient-subjects. Informed consent, aimed at promoting autonomy and protecting the individual subject, crumbles when research participation is offered in a clinical setting. Fortright discussion and deliberation requisite for meaningful consent is unlikely when patients suffer from a therapeutic misconception and when competing interests, namely those of the scientific community and those of society, exist. The medical community thus must embrace the need to subject certain research trials to greater scrutiny, and informed consent must be revamped. A few monolithic standards and regulations guiding procurement of consent are insufficient. Researchers must consider the unique needs and vulnerabilities of different groups and adjust the consent process to respond better to modern research such as gene therapy.

To demonstrate the inadequacies of informed consent in the contemporary context and the need for better subject protection, this paper begins by scrutinizing the rise of modern informed consent doctrine in international legal documents as well as in the United States arena. After examining the federal regulatory framework governing experimentation with human subjects, considerable attention is given to the doctrine of informed consent and its shortcomings in the research setting, including lack of competence to grant consent, misunderstandings and conflicts of interest between researcher and subject, and the doctrine's incompatibility with several dynamics of the patient-physician encounter. Flaws pertaining to both the research and therapeutic settings are also noted. IRBs' responsibilities for protecting subjects are then explored, along with the numerous factors preventing these bodies from providing adequate safeguards. The paper then discusses current regulations regarding various groups- the terminally ill, women, children, prisoners, and the decisionally/cognitively impaired, including psychiatric patients and the elderly- as well as considera-

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tions unique to each. This uncovers shortcomings of current informed consent doctrine and illustrates that meaningful consent can only be achieved by crafting procedures and policies specifically tailored to the needs of each particular population. Next, problems that modern medical research in the gene therapy area raises are probed, and numerous proposals to ameliorate the informed consent process as well as IRB efficacy are offered.

### The Rise of Human Experimentation Regulation in the International and National Arenas

Legal proceedings in 1947 against Nazi doctors who subjected volunteers to epidemics such as malaria and typhus, injection with poisons, sterilization, and to various other atrocities led to the announcement of contemporary ethical principles to govern international research standards, known as the Nuremberg Code. The Code, consisting of ten principles of human experimentation, flagged the dawn of heightened scrutiny of human subject experimentation.<sup>9</sup> Its most frequently cited provision is the first:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have

sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an under-

standing and enlightened decision. This . . . requires that before the acceptance of an affirmative decision by the experimental subject

there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to

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<sup>9</sup>It may be plausibly argued that public debate in the United States did not immediately ensue. Not until Henry Beecher's article did the government begin to confront ethical issues pertaining to human subject experimentation. For example, the Supreme Court rejected the opportunity to adopt Nuremberg Code principles. See Karine Morin, *The Standard of Disclosure in Human Subject Experimentation*, 19 J. LEGAL MED. 157, 157 n.1 (1998).

be conducted; all inconveniences and hazards reasonably to be expected, and the effects upon his health... which may... come from his participation...<sup>10</sup>

Placing this ideal in text proved significant in the wake of the Second World War, during which the United States committed egregious abuses of individual rights. While the notion of consent had played a role in American research ethics and law since the 1830's, it was not until the Code that consent principles were formally reduced to writing.<sup>11</sup> Consent of the subject is necessary but not sufficient under the Code, whose other guidelines pertain to the welfare of subjects, must be met prior to the seeking of consent, and cannot be waived.

While the Judges at Nuremberg intended universal application of the document, which remains the most authoritative script setting international research standards and one of the most eminent human rights manifestos, it has fallen short of its aims. The Code is often regarded as a response to Nazi terror and trivialized as a context-bound relic no longer helpful in the modern research milieu. Critics contend that the document proves too demanding, fails to recognize the ideals of scientists, and that its absolutism cannot operate in conjunction with the impersonal and utilitarian ethics of contemporary medicine.<sup>12</sup> Furthermore, uncertainty arises from the Code's opening line stating that voluntary consent of the subject is essential by seemingly precluding experimentation with emergency patients, children, and the decisionally impaired.

Due to such shortcomings, the World Medical Association has endeavored to unfrock the Code with the Declaration of Helsinki, promulgated in 1964 and subsequently revised three times. The Declaration consists of recommendations by physicians to their peers and aims to displace the human rights-based goals of the

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<sup>10</sup>THE NUREMBERG CODE, *quoted in* Morin, *supra* note 9, at 172.

<sup>11</sup>*See* S. Rebecca Holmes-Farley and Michael Grodin, *Foreword: Law, Medicine, and Socially Responsible Research*, 24 AM. J. L. & MED. 153, 153 (1998).

<sup>12</sup>*See* Garnett, *supra* note 6, at 472-73.

Code with a more indulgent medical ethics agenda tolerating paternalism. Amendments to the document dropped references to informed consent and added that physicians need not secure a subject's consent to medical research combined with professional care if they submit a reason for not obtaining consent to an independent review committee. The Declaration is most notable, however, for beginning to blur the line between treatment and research by bifurcating research into therapeutic and nontherapeutic, a distinction referring to whether or not it may prove directly beneficial to the subject. With respect to research on terminal illnesses such as AIDS, this distinction means that research will be deemed therapy. A drawback of the Declaration as well as the Code it sought to supplant is that both are merely hortatory; neither possess legal status in most countries nor furnish sanctions or enforcement mechanisms. Both have been condemned as extremely ambiguous, representing nothing more than 'pious hopes' that doctors will behave ethically.<sup>13</sup> In this country, disregard for groups such as prisoners, the elderly, and the mentally disabled in no way subsided in the wake of the Nuremberg Code and Declaration of Helsinki. Scrutiny of contemporary human experimentation in the United States reveals that enforceable domestic regulation was necessary to curb abuses. The government endorsed regular testing of vaccines for the military on the mentally disabled without their consent during the Second World War, offering feckless utilitarian justifications for experiments contravening human dignity. In 1952-3, an inmate of the New York Psychiatric Institute also died at the hands of the government, a casualty of the institution's secret contract with the Army Chemical Corps to conduct research employing a mescaline derivative. The Atomic Energy Commission simultaneously financed studies to demonstrate non-belligerent uses of nuclear energy. In one experiment, investigators used emotionally disturbed adolescent boys in Massachusetts institutions to examine mineral intake in the human body by employing minute amounts of radiation in breakfast cereal as a tracer. At one such institution,

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<sup>13</sup>Sharon Perley et al., *The Nuremberg Code: An International Overview*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION*, at 149, 160 (George J. Annas and Michael A. Grodin, eds., 1992), *quoted in* Ileana Dominguez-Urban, *Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally*, 30 *CORNELL INT'L L.J.* 245, 274 (1997).



researchers asked parents to consent to their child's participation in a special program entitled the science club without being told its true purpose, that ingestion of radiation would occur, and that the research offered no prospect of medical benefit.<sup>14</sup> Another flagrant research abuse that extended no direct benefit to subjects nor contributed to knowledge of their impairment occurred in 1963 with decisionally impaired patients at the Brooklyn Jewish Chronic Disease Hospital, where debilitated residents received live cancer cell injections without their knowledge. Investigators seeking to gain an understanding of the manner in which patients with non-cancerous chronic conditions respond to the presence of transplanted cells argued that failure to seek consent had occurred in more dangerous procedures and that they feared frightening patients. Other contemporary ethically questionable experiments involved a contraceptive study using impoverished Mexican-American women who were assured they would receive birth control when half received placebos and a hepatitis study using inmates of an institution for developmentally disabled children.

In 1966, Henry Beecher authored a landmark article in the *New England Journal of Medicine* drawing attention to a formidable list of unprincipled research being conducted at the nation's most elite universities. Discovery of events such as the Tuskegee studies of 1932-72, in which researchers seeking to ascertain the death rates for untreated cases of syphilis recruited infected black men by promising free treatment but actually charted the progress of their disease and let them die,<sup>15</sup> also produced considerable controversy. The two events spurred development of federal regulations now governing the conduct of human research.

Senate hearings on human experimentation and the passage of the National Research Act of 1974 made the mid-1970's the dawn of a more comprehensive federal policy on research ethics. This legislation established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,

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<sup>14</sup> See Jonathan D. Moreno, *Regulation of Research on the Decisionally Impaired: History and Gaps in the Current Regulatory System*, 1 J. HEALTH CARE L. & POL'Y 1, 9 (1998).

<sup>15</sup> Adding to the egregiousness of the study was the denial of treatment after the invention of penicillin in 1947 and the dissuasion of the subjects from seeking services where they might receive treatment with penicillin for other conditions. See Holmes-Farley and Grodin, *supra* note 11, at 187.

which identified basal ethical precepts that would underlie human research and suggested guidelines for studies that the then Department of Health, Education, and Welfare supported. The fruit of its efforts yielded the 1979 Belmont Report, which considers the line to be drawn between the practice of biomedical therapy and research and announces the principles of respect for persons, beneficence, and justice as especially significant to experimentation with human subjects. The Report explains that respect for persons involves persons being treated as autonomous agents and individuals with diminished autonomy being entitled to protection. Beneficence mandates that the harm threatening subjects in a particular study or in the entire enterprise of research be minimized or mitigated through affirmative efforts to secure patients' well-being.<sup>16</sup>To apply these principles, the Report requires informed consent, risk/benefit assessment, and the appropriate selection of subjects of research as well as equitable distribution of benefits of research. For truly informed consent, the Report mandates that subjects be furnished with enough information, such as the research procedure, its purpose, potential risks and benefits, the existence of alternative procedures, and statements offering the opportunity to raise questions and to withdraw from the study at any time, to choose an appropriate course.

The Report, does not, however, address what quantum of information should be provided. Furthermore, much research may be justified even when subjects are not the direct beneficiaries of the research if participation in research may lead to both the increase of knowledge as well as to the development of improved procedures.<sup>17</sup>Finally, the National Research Act requires that every body applying for a grant or contract implicating biomedical or behavioral research using human subjects submit assurances satisfactory to the Secretary of Health, Education, and Welfare that it has established an IRB to review the project and to safeguard subjects' rights. The Report thus announces a doctrine of informed consent with similar re-

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<sup>16</sup>See Jesse Goldner, *An Overview of the Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 97 (1993).

<sup>17</sup>See *id.*

quirements for therapy and research, the only difference being that the process for the latter involves IRB scrutiny. Because experimentation occurs in the realm of the unknown and unproven, however, numerous features differentiate it from treatment: risks may not be easily identifiable, a subject's consent cannot be grounded on anticipated benefits, researchers and subjects may have diverging interests, and assumptions are unsubstantiated by scientific evidence. Expertise in this realm is thus more vulnerable than in clinical practice.<sup>18</sup> The Belmont Report's legacy proves remarkable, for the document's distinction between research and therapy has shaped informed consent ever since its formulation. While federal regulations guiding human subject research manifest theoretical foundations in the Belmont Report, they struggle with scenarios involving aspects of both research and therapy. Confusion thus arises about how to categorize interventions defying strict categorization and increases when [research] is conducted on sick subjects because such research routinely takes place in a clinical setting, where the atmosphere is more conducive to a focus on the patient's trust of the physician and sometimes less attentive to the subject's right to a full disclosure of information.<sup>19</sup> As federal funding for scientific research increased in the decade prior to the Belmont Report, FDA and Department of Health and Human Services (hereafter DHHS) also heightened their regulatory involvement in human research, translating experimentation into a tightly controlled enterprise. As the regulations currently stand, the 1991 common Federal Policy for the Protection of Human Subjects<sup>20</sup> governs activities which any of seventeen federal departments and agencies sponsor. Known as the Common Rule, the Policy codifies 1981 enactments of DHHS regulations which honor the principle of autonomy in informed consent. DHHS supervises protection of human research subjects utilizing review at the federal and institutional levels, and to receive research funds, institutions must guarantee in writing that investigators will

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<sup>18</sup>See Morin, *supra* note 9, at 213.

<sup>19</sup>Larry R. Churchill, Myra L. Collins, Nancy M.P. King, Stephen G. Pemberton, and Keith A. Wailoo, *Genetic Research as Therapy: Implications of Gene Therapy for Informed Consent*, 26 J.L. MED. & ETHICS 38, 39 (1998).

<sup>20</sup>See 45 C.F.R. §46.101-.409 (1997).

heed ethical principles of the Belmont Report and requirements of §45 C.F.R. 46. These regulations delineate general protections for all human subjects and additionally permit IRBs to implement supplemental safeguards for experiments involving vulnerable populations.<sup>21</sup> They do not, however, reach privately funded research. Regulations promulgated under the Food, Drug, and Cosmetic Act govern such study aimed at introducing a new drug or medical device to market. Additionally, all domestic clinical trials involving investigational drugs are under FDA oversight, regardless of funding source. The joint effect of DHHS and FDA regulations proves significant, for federal policy thus controls most human subject and drug research performed domestically.<sup>22</sup> Because society now views exclusion from research as discriminatory denial of beneficial treatment,<sup>23</sup> federal agencies must contend with demands to loosen research requirements. Related to such calls for relaxation are concerns that certain populations, such as women and children, have been systemically banished from protocols and thus cannot reap benefits emanating from research. Furthermore, the practice of experimenting with the desperately ill has fashioned favorable views among clinicians and patients about therapeutic merits of research. Regulators have responded by hastening the approval process for promising treatments for life-threatening illnesses, easing access to unapproved therapies, and allowing desperate use guidelines for gene transfer research. Each of these regulatory responses remove unproven interventions from the category of research into that of therapy in certain circumstances.

### Informed Consent and Its Flaws

The fundamental tenet of informed consent maintains that research may not be performed unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized

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<sup>21</sup>See 45 C.F.R. §46.109 (1997).

<sup>22</sup>It should be noted that numerous additional controls operate to regulate the conduct of research apart from those which directly involve interaction with human subjects. Individual institutional policies, for example, often demand disclosure or prohibition of financial conflicts of interest, and other federal regulations require suspension of eligibility for financial assistance of organizations and individuals who commit financial abuse. See Goldner, *supra* note 16, at 89.

<sup>23</sup>Churchill et al., *supra* note 19, at 40.

representative.<sup>24</sup> Although the researcher must provide an IRB-approved consent form, he may freely discuss the experiment with the patient, explain terms employed in the consent form, and address any queries of the subject without Board monitoring. As noted in discussion of the Belmont Report, informed consent for research is mandatory, yet its incompleteness or comprehensiveness in therapeutic settings varies with the individual physician. In the latter milieu, physicians are expected to attend only to the welfare of the individual before them. The doctrine itself is rooted in fundamental values such as autonomy, individuality, bodily integrity, leading one commentator to note that [i]nformation is power and because information-sharing inevitably results in decision-making sharing, . . . informed consent has helped transform the doctor-patient relationship.<sup>25</sup> Other aims of informed consent include elevation of rational decision-making, prevention of fraud and duress, promotion of self-scrutiny by the physician-investigator, and involvement of the public in significant issues of health care research and policy. It aims to enrich the physician-patient relationship in treatment decisions, envisioning an active patient role made possible by informed consideration, deliberation, and choice.

Informed consent, then, succeeds only when subjects are fully apprised of the potential dangers they chance. Regulations thus mandate that risks, benefits, and alternatives to participation be described and that patients be advised of procedures that would not be performed but for the research.<sup>26</sup> Subjects are also to be told in lay language that a project involves research and advised of the nature of privacy protections as well as the appropriate person to consult with any questions.<sup>27</sup> Additionally, researchers must clarify that participation is voluntary and that refusal to participate will not adversely affect the potential subject.<sup>28</sup>

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<sup>24</sup>45 C.F.R. §46.116 (1985).

<sup>25</sup>GEORGE J. ANNAS, THE RIGHTS OF PATIENTS: THE BASIC ACLU GUIDE TO PATIENT RIGHTS 83 (1989), *quoted in* Morin, *supra* note 9, at 159.

<sup>26</sup>*See* 45 C.F.R. §46.116(a)(2)-(4).

<sup>27</sup>*See* 45 C.F.R. §46.116(a)(5) and (a)(7).

<sup>28</sup>*See* 45 C.F.R. §46.116(a)(8).

One standard justification for such disclosure obligations is that dangers of research cannot be ascertained in advance. Experimental settings, more so than those in which standard medical treatments are dispensed, pose unknown. . . degrees of risk. . . [so] there must be broad allowance for personal, idiosyncratic preferences and values.<sup>29</sup> Since medical expertise by definition does not exist in research contexts, patients possess no reason to defer to it. No one proves a better expert than the patient in resolving the core moral concern of experimentation, i.e. whether he should volunteer his body to augment medical knowledge.<sup>30</sup> Furthermore, experimentation often confers little or no gain upon the subject. Informed consent reflects a judgment that most patients possess sufficient capacity to comprehend, evaluate, and render decisions regarding their medical condition and future. Unless evidence suggests otherwise, competence to consent is presumed in most instances.

Numerous factors, however, work to undermine patients' abilities to understand, balance, and render decisions, diminishing their competency to consent. The process of informed consent occurs at a time when unease often threatens to compromise it. Illness can interfere with a subject's routine thought processes and hinder him from reaching responsible conclusions. This consideration proves all the more problematic when stress, pain, side effects of drugs, or fear accompanies sickness. Ramifications of an ailment itself may bring about diminished competence, and physical and emotional consequences of illness may additionally influence a patient's perception of information disclosed. Clinicians, then, may be justified in thinking that it is foolish to approach any patient as a capable joint participant in decision-making.<sup>31</sup> While problems in informed consent may well emanate from inadequate or nebulous disclosure, shortcomings are likely to arise due to the doctrine's failure to regard competence as present in degrees, varying over time and under different con-

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<sup>29</sup>Richard Delgado and Helen Leskovic, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67, 88-89 (1986).

<sup>30</sup>See *id.* at 90.

<sup>31</sup>Frank W.S.M. Verheggen, *Myth and Reality of Informed Consent in Clinical Trials*, 16 MED. & L. 53, 59 (1997).

ditions. Federal regulations largely disregard the process by which patients evaluate information presented to them and supply a generic presumption rather than specific criteria for assessing competence.<sup>32</sup> Because it involves assessments of numerous considerations, competence cannot be easily determined. To view consent as fulfilled once information has been furnished proves problematic, however, since it wholly ignores underlying processes of deliberation.

Inability of the patient to comprehend that motives of physician-investigators conflict with his own in the research setting likewise seriously undermine informed consent's goals. The presence of doctor-investigators in white coats may lead to mistaken subject beliefs that research being performed is for one's own benefit. Traditionally, the doctor-patient relationship has been characterized as a fiduciary one premised on honesty, confidence, and good faith. Notions that physicians in therapeutic settings endeavor to achieve as much as possible for the individual patient seeking medical assistance and that the professional's recommendations are trustworthy endure. Patients' confidence in the beneficence of physicians cause the former to regard invitations to participate in research as professional recommendation[s] . . . intended to serve . . . individual treatment interests.<sup>33</sup> This conviction hinders patients from appreciating that in research, unlike therapy, the research question proves primary:

It is unlikely that patients can ever see the distinction between physician and researcher, because most simply do not believe that their physician would either knowingly do something harmful to them, or would knowingly use them simply as a means for their own ends.<sup>34</sup>

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<sup>32</sup>*Id.* at 60.

<sup>33</sup>Jay Katz, *Human Experimentation and Human Rights*, 38 ST. LOUIS U. L.J. 7, 29 (1993).

<sup>34</sup>George J. Annas, *The Changing Landscape of Human Experimentation: Nuremberg, Helsinki, and Beyond*, 2 HEALTH MATRIX 119, 130-31 (1992).

Patients often fail to differentiate between experimentation and therapy, and those with a poor prognosis may esteem research as a treatment option. The manner in which a physician-investigator presents the possible advantages of research to a subject affects the degree to which the latter misconstrues the nature of his participation in a study. Patients thus fail to recognize that the ideology of professionalism, which allows doctors considerable discretion in rendering decisions for patients due to faith that physician self-interest will succumb to patients' interests, cannot be applied to clinical research situations since physician-investigators harbor dual allegiances to subjects as well as the research protocol. Medical professionals confront the difficult dilemmas of seeking truth for science, beneficence for the patient, and self-interest as an individual investigator.<sup>35</sup> Several other dynamics of the physician-patient encounter likewise highlight deficiencies in the current formulation of informed consent. Permeating the doctor-patient relationship are authoritarian overtones; the assertion that patients cannot comprehend esoteric medical information has often been used to justify doctors' command over patient needs. Because informed consent's underlying assumption- i.e. that patient autonomy merits respect- has been alien to the physician mindset throughout medical history,<sup>36</sup> the doctrine has not significantly tempered physician authority in the decision-making process. Independence of physicians has been preserved at the expense of patients. A power differential exists even between the most decisionally capable, sophisticated subject and an investigator, and inevitably the researcher is on top, and the patient-subject is on the bottom.<sup>37</sup> This discrepancy is a product of a patient weakened by disease and a researcher possessing a superior grasp of the relevant medical knowledge. As an affliction grows more serious, the power imbalance grows more extreme; worsening disease yields desperation, which can render patients susceptible to manipulation. Further aggravating this situation is the fact that subjects are often recruited

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<sup>35</sup> See Katz, *supra* note 33, at 30.

<sup>36</sup> See *id.* at 20.

<sup>37</sup> Evan G. DeRenzo, Robert R. Conley, and Raymond Love, *Assessment of Capacity to Give Consent to Research Participation: State-of-the-Art and Beyond*, 1 J. HEALTH CARE L. & POL'Y 66, 77 (1998).



from different age and demographic groups than researchers, typically from those enjoying less power and economic status than investigators.

Such factors contribute to potential for those holding knowledge to abuse their power, dismiss patients as irrational, and thus justify paternalism and beneficence rather than subject autonomy as controlling guides for research conduct. Even physicians theoretically dedicated to securing patient consent concede that, in practice, they exercise laxity in informed consent. Their invitation to a patient to participate is a result of an already completed, careful consideration of the project's risks and benefits as well as their conclusion that no harm will come to the patient. Thus, investigators may elusively address patient concerns and suggest that participation is expected or that nontrivial risks are minimal.

Differences between investigator and patient prove so substantial that the former often fails to regard the patient as patient, but rather only as a subject. Scientific dedication to objectivity causes investigators' thought processes to become objectified, transforming human beings under study into data points to be plotted on a chart that will prove or disprove a research hypothesis.<sup>38</sup> As cancer researcher James Holland comments,

Patients have to be subsidiaries of the trial...I'm not interested in holding patients' hands. I'm interested in curing cancer... Every patient becomes a piece of scientific data.<sup>39</sup>

It cannot be doubted, however, that the majority of Holland's patients seek a cure and regard him as their physician, not merely as a scientist. In this scenario, then, the Declaration of Helsinki's distinction between therapeutic and non-therapeutic proves empty. Researchers additionally manifest objectivizing tendencies

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<sup>38</sup>Katz, *supra* note 33, at 33.

<sup>39</sup>Dena Kleiman, *In Search for a Cancer Cure, Patients Come Second*, N.Y. TIMES, February 18, 1986, at B1, B7, *quoted in* Annas, *supra* note 34, at 131.

in their interest in a new treatment's upshot in terms of longevity, while patients often are harbor quality of life concerns. Furthermore, objectification may grow more extreme through influence of attitudes on race, creed, gender, socioeconomic standing, and the scientific imperative of the research.<sup>40</sup> It should also be noted that medical research greatly differs from the doctor-patient relationship, traditionally deemed a private, one-on-one concern. A physician-investigator scarcely becomes acquainted with the patient-subject, and research fellows, nurses, or non-physician associate investigators may secure consent. The objectification process thus reinforces diverging values which exist between physician and patient and which may impact decision-making.

Aside from the aforementioned difficulties the research setting poses for efficacy of informed consent, more general shortcomings also present in the therapeutic context- routinization and costs as well as difficulties of disclosure- undermine the doctrine's goals. Legal medical ethicist Jay Katz argues that in the clinical milieu, doctors have never accepted informed consent as a route to recognizing patient autonomy, instead merely tolerating it as a requisite legal duty:<sup>41</sup>

The result is too often a form of Mirandizing, in which consent for routine patient care is seen as a legal encumbrance, introduced with words such as, We have to consent you now.<sup>42</sup>

Such routinization endangers consent in an era when it is most needed, i.e. when investigators oversell gene therapy research to patients and the media. Consent is likewise jeopardized due to its costs: the process proves time-consuming, and ensuring that patients genuinely understand what a study entails and why ne-

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<sup>40</sup>See Katz, *supra* note 33, at 33.

<sup>41</sup>See Jay Katz, *THE SILENT WORLD OF DOCTOR AND PATIENT 2* (New York Free Press, 1984), *quoted in* Churchill et al., *supra* note 19, at 42.

<sup>42</sup>Churchill et al., *supra* note 19, at 42.

cessitates more effort than doctors believe they can reasonably invest. Another difficulty emanates from the requirement that professionals disclose alternatives. If the alternative is a treatment that doctor does not recommend, uncertainty may surround whether the option should be disclosed. Physicians often do not wish to furnish patients and families with information concerning experimental procedures, concerned that awareness of an alternative to death is inherently coercive.<sup>43</sup> Divulging alternatives may open patients to situational coercion, leaving them incapable of exercising free and informed choice because of societal pressure to exhaust all possible measures. Thus, when no standard therapy exists, some doctors prefer to promote acceptance of a fatal outcome rather than to suggest experimental technology.<sup>44</sup> Disclosure itself derives meaning from investigators. Those deeming novel technologies promising rather than experimental mold disclosure differently than those who evaluate experimental procedures more cautiously. Disclosure also proves problematic when a researcher provides too much information; if asked to digest huge quantities of complex knowledge, a patient will be overwhelmed rather than educated and cannot ask questions because he does not understand enough even to formulate them. Striking a balance in terms of the quantum of information to disclose is difficult, for a doctor who reveals too little out of concern for encumbering a patient may foreclose the latter's ability to make decisions in which his needs are inconsistent with that which the physician thinks best. Additionally, the situation in which disclosure occurs merits attention. When consent is sought under humiliating or insulting conditions, it cannot be labeled informed. The net result of aforementioned considerations is generally informed compliance as opposed to informed consent: doctors render decisions concerning the type of treatment patients should have and then supply whatever information in whatever setting is necessary for assent.<sup>45</sup> The legal system's failure to afford effective remedies to patients

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<sup>43</sup>King and Henderson, *supra* note 4, at 1041.

<sup>44</sup>For example, heart transplantation and surgical palliation of hypoplastic left heart syndrome is a last resort measure to treat a defect that is inevitably fatal, usually within weeks. One doctor expresses concern that if she reveals the procedure's availability to parents, they will feel pressured to pursue it and experience guilt if they do not try everything possible to save their child's life. See King and Henderson, *supra* note 4, at 1036.

<sup>45</sup>See Katz, *supra* note 33, at 17 n.34.

injured by inadequate informed consent further contributes to the doctrine's impotence. Consent regulations provide no adequate remedy to patient-subjects for a researcher's or institution's breach. While subjects suffering harm in the course of research due to a failure to obtain informed consent may receive medical and psychological treatment from the institution, regulations do little for victims of unconsented-to study. While some argue that a private cause of action can be inferred from the regulations,<sup>46</sup> no appellate court has addressed this possibility. No court yet has provided recourse for infringement upon a subject's right of choice without physical or emotional injury, suggesting that current case law cannot sufficiently safeguard subjects' rights to informed consent. Courts appear recalcitrant to place sanctions on researchers who are experts in their fields and endeavor to better medical and social science.

Whereas compensatory justice mandates that society indemnify subjects for research-related injuries since they assume a position of risk on behalf of society,<sup>47</sup> patients experience tremendous difficulty obtaining legal redress since determining the scope of required disclosure proves problematic for courts. To establish physician negligence in obtaining consent, a plaintiff must demonstrate that a patient-physician relationship existed, a physician had a duty to disclose certain information, the physician failed to provide this information, and the failure to do so cannot be excused. A showing must additionally be made that if the professional had provided the patient with the undisclosed information, the patient would not have consented to treatment, and that the failure to disclose constitutes the proximate cause of injury and damages claimed.<sup>48</sup> Causation often is the most difficult element to prove, established when the injured can demonstrate that he would not have assented if proper disclosure occurred. Negligent disclosure, furthermore, is determined in many states according to a professional standard. Disclosure is thus often viewed as a concern

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<sup>46</sup>Delgado and Leskovac, *supra* note 29, at 80.

<sup>47</sup>See James F. Childress, *The National Bioethics Advisory Commission: Bridging the Gaps in Human Subjects Research Protection*, 1 J. HEALTH CARE L. & POL'Y 105, 117 (1998).

<sup>48</sup>See Morin, *supra* note 9, at 160.

of medical judgment, determined by what a reasonable physician under the same circumstances would reveal.

### Institutional Review Boards and Their Shortcomings

Like informed consent, IRBs seek to safeguard the welfare and rights of subjects. DHHS regulations mandate that proposed clinical research undergo review of an IRB, a body which determines whether and on what terms medical experimentation involving human beings may be conducted. Boards function as peer review committees ensuring that research studies are scientifically sound, well-designed, safe, and that potential benefits outweigh possible risks those under study. To perform such duties, these bodies must be composed of members with sufficient scientific expertise to appraise the research protocol as well as the researcher's abilities. In reviewing experiment proposals, IRBs must determine that dangers to the subject are minimized, selection of subjects is equitable, risks are reasonable in relation to anticipated benefits, appropriate informed consent will be secured and carefully documented for each subject, and that if necessary, the research plan will include monitoring of data.

Boards are expected to consider the nature, content, and design of the study, ethical guidelines of the Belmont Report, and where appropriate, the regulatory mandates of DHHS and FDA.<sup>49</sup> IRBs also must conduct a continuing review of every study at least annually as well as check the informed consent document provided to each subject, ensuring it contains all factors mentioned in federal regulations. They may, however, waive the informed consent requirement for research entailing only minimal risk if the waiver will not adversely impact subject rights and welfare.<sup>50</sup> Boards additionally must also heed specific regulations affording additional protections to research involving vulnerable subjects, i.e. children, prisoners, pregnant women, [and] handicapped or mentally disabled persons.<sup>51</sup> Federal guidelines suggest that IRBs exercise special caution

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<sup>49</sup> See 45 C.F.R. §46.103.

<sup>50</sup> See 45 C.F.R. §46.117(c).

<sup>51</sup> See 45 C.F.R. §46.107(a) (1992).

in safeguarding the interests of these subjects by including an individual knowledgeable and experienced in working with these subjects<sup>52</sup> as one of its members.

Because IRBs act as representatives of the broader local community acceptance of an experiment's particular risk/benefit ratio, federal regulations also devote attention to the composition and operating procedures of such bodies. IRBs must consist of at least five individuals of varying backgrounds. One must possess primarily scientific interests, one must hold primarily nonscientific interests, and one must lack affiliations with the research institution. A quorum, with at least one member whose concerns are nonscientific, must be present for any vote. Diverse membership aims to safeguard the rights and welfare of subjects effectively; detailed rules additionally mandating that [e]very... effort be made to ensure that no IRB consists entirely of men or entirely of women and that more than one profession be represented further this goal.<sup>53</sup> Lay members theoretically function as watchmen, defending against excessive zeal of scientists and providing a link with the norms of the local population. A majority of IRB members rather than subcommittees or delegates, furthermore, must study research proposals at regularly scheduled meetings. IRBs thus reflect a judgment that medical progress should move forward, yet without relegating the interests of human study participants. IRBs as currently configured, however, protect the institution and its investigator rather than shield research subjects. The majority of the Board's members serve on the faculty of the institutions to which the investigator belongs. Not only do these individuals share concerns and objectives similar to those of the investigator, but they also recognize that just as they now sit in judgment of a research proposal, their own protocols will be subjected to the same scrutiny. It thus proves improbable that Board members will demand from other experimenters a standard of disclosure and consent that insulates human research subjects if doing so will tighten the conduct of research. IRBs therefore do not address problems common to many studies, including

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<sup>52</sup> *Id.*

<sup>53</sup> 45 C.F.R. §46.107(b)-(d) (1992).

inadequate differentiation between trivial and non-trivial risks, manipulation of subject consent, insufficient highlighting of the severity of foreseeable risks and nondisclosure of their probability, scant discussion of risks and benefits of non-participation,<sup>54</sup> and consent forms which inflate possible benefits or are otherwise deficient.

Boards typically strictly focus on risk-benefit ratios as well as on consent forms, rendering them less likely to promote meaningful consent. Approved consent forms often do not furnish relevant information in understandable language, and an IRB that determines that research poses only minimal risk and subsequently waives the consent requirement deprives the subject of any role in deciding whether risks are minimal or of his desire to be advised of possible trivial risks. Federal regulations thus implicitly allow researchers and IRBs to choose when a prospective human subject may exercise his autonomy.<sup>55</sup> Furthermore, IRB focus on consent forms and requirements contribute to little evaluation of the merits of research, a deficiency also attributable to members bearing institutional loyalties who get caught between desires to safeguard subjects and to advance their institutions. Composition of the IRB itself likewise promotes institutional rather than subject concerns, for dominance by researchers fosters a systematic bias favoring experimentation. As Professor Robert Veatch explains, it also proves difficult to involve a scientifically-dominated group in assessment of whether a research protocol accords with standards of community acceptance:

The problem is not one of lacking confidence or trust in the goodwill of the scientists. Trusting scientists to decide about the value of knowledge is a bit like trusting a rabbi friend to pick a good Easter ham. He is to be trusted as a person of goodwill, but he is simply not the appropriate person to ask.<sup>56</sup>

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<sup>54</sup>See Katz, *supra* note 33, at 51.

<sup>55</sup>See Delgado and Leskovic, *supra* note 29, at 123.

<sup>56</sup>Robert Veatch, THE NATIONAL COMMISSION ON IRBs: AN EVOLUTIONARY APPROACH, 9 HASTINGS CTR. REPORT 22, 26 (1979), *quoted in* Goldner, *supra* note 16, at 106.

Additional shortcomings of IRBs emanate from changes in the research environment as well as increased workloads. The current framework for IRB practices was fashioned in the 1970's, when one investigator usually performed research and worked under government funding with a small group of human subjects in a university teaching hospital.<sup>57</sup> Contemporary experimentation, however, is quite different due to increased commercialization and private funding of research, explosion of managed care, use of multi-site trials, an increase in patient consumerism, and escalating numbers of research protocols.<sup>58</sup> Such changes have placed tremendous strains on IRBs, which have acquired additional responsibilities and mountains of paperwork. Boards must now grapple with complex novel issues bearing significant societal implications, such as genetic research. Resource constraints combine with these factors to render IRB monitoring of a study's progress following approval virtually nonexistent and to preclude Boards from going beyond their most perfunctory requirements. Federal guidelines promote a rushed atmosphere where thoughtful evaluation often proves impossible, and Boards inundated with protocols and adverse event reports cannot devote sufficient attention to each review.<sup>59</sup> These bodies rarely perform on-site monitoring of research conduct, relying on an honor system. They are also largely incapable of monitoring possible conflicts of interest of researchers, a problem plaguing gene therapy experiments.

Aforementioned hardships facing IRBs contribute to their inability to protect vulnerable subjects unable to defend their own interests in the informed consent process. No national consensus or consistent guidelines exist, for example, on what constitutes proper safeguards for individuals with progressive dementias such as Huntington's and Alzheimer's diseases.<sup>60</sup> Thus, cognitively impaired research subjects must look to IRBs

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<sup>57</sup>See DEP'T OF HEALTH & HUM. SERVICES, OFF. OF INSPECTOR GEN., PROTECTING HUMAN RESEARCH SUBJECTS: STATUS OF RECOMMENDATIONS 22 (April 2000).

<sup>58</sup>See *id.*

<sup>59</sup>See *id.*

<sup>60</sup>See Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, 1 J. HEALTH CARE L. & POL'Y 88, 94 (1998).



for protection. Consequently, Boards should devote special care to considering the nature and degree of impairment, prospective risks and discomforts of participation, and the potential for direct benefit to the individual subject. Increased workloads, resource constraints, and problems created by institutional loyalties, however, preclude IRBs from making such careful determinations. Significant evidence suggests, for example, that Boards are unlikely to compensate for the lack of particular regulations pertaining to the cognitively impaired through a proactive use of their discretionary authority.<sup>61</sup> IRBs do not review the details of investigator-subject interaction, thus depriving groups especially vulnerable to coercion of much-needed protection and devoting inadequate attention to these groups' assumptions of trust in physician-researchers.

### The Terminally Ill

Federal regulations do not classify the terminally ill as a vulnerable population, yet thorny consent issues arise from the fact that many research subjects are vulnerable merely because they are ill. Individuals suffering from malignant disorders or plagued by ailments refractory to other treatment often desperately seek inclusion in clinical trials evaluating the efficacy of novel drugs and drug combinations as well as of uncorroborated practices. Vulnerability of such patient-subjects varies with the gravity of illness as well as their degree of desperation. Cancer and AIDS, for example, arguably are the two most feared ways of dying in the developed world, perceived not just as lethal, but as dehumanizing, literally so.<sup>62</sup> A terminal diagnosis itself shapes what researchers as well as patients regard as reasonable, both often believing that the dying person has nothing to lose. In confronting certain illnesses, it additionally proves impossible for a researcher to render the requisite boilerplate language of the federal regulations candidly, as experimental therapies are the only available treatments and refusal to participate without penalty, i.e. imminent death, is impossible. Even if consent forms possess clarity and accuracy, conversations with patients may render issues nebulous.

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<sup>61</sup>See Jonathan D. Moreno, *supra* note 14, at 14.

<sup>62</sup>SUSAN SONTAG, AIDS AND ITS METAPHORS 126 (1989), *quoted in* Annas, *supra* note 34, at 127.

Desperately ill subjects may selectively listen, absorbing only facts about prospective benefits, and investigators anxious to recruit volunteers may address risks in a cursory manner. Dying persons thus may not truly be free to render autonomous decisions, captive to their disease and thus under coercion of their illness and potentially of others. As a former editor of *The New England Journal of Medicine* observes, the thumb screws of coercion are most relentlessly applied [to] the most used and useful of all experimental subjects, the patient with disease.<sup>63</sup> Likewise, as a one's disease grows more severe, his capacity to retain information from the consent procedure decreases.

Diagnosis of a terminal illness usually spurs a significant psychological reaction in patients and sometimes causes a variety of psychopathologies.<sup>64</sup> Physiological symptoms may exacerbate psychological hardships. This combines with patients' reluctance to question their physicians to reduce the capability of a terminally ill patient to engage in autonomous, rational decision-making. Cancer patients, for example, commonly experience sentiments of inadequacy, fear, anxiety, confusion, and hopelessness, dreading the six D's: dependency, death, disfigurement, disability interfering with normal life functions, disruption of relationships, and discomfort or pain resulting from the disease. Their disease itself may directly hinder cognitive ability: fatigue, toxicity of medication, and recovery from radiation can impair the speed and quality of thought processes. One who is hospitalized for an extended period of time may additionally respond to his environment in a manner hindering his ability to render informed decisions. Sleep deprivation commonly associated with hospital stays, for example, exaggerates the emotional and physical trauma of terminal illness and may create confusion, disorientation, and memory disturbance.<sup>65</sup> Just as prisoners prove wholly dependent on guards and other jail employees for their well-being, the terminally ill often depend completely on hospital

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<sup>63</sup>F.J. Ingelfinger, *Informed (But Uneducated) Consent*, 287 NEW ENG. J. MED. 465, 466 (1972), *quoted in* Annas, *supra* note 34, at 127.

<sup>64</sup>See D. Christian Addicott, *Regulating Research on the Terminally Ill: A Proposal for Heightened Safeguards*, 15 J. CONTEMP. L. & POL'Y 479, 496 (1999).

<sup>65</sup>See *id.* at 501.

staff and researchers. Consequently, such patients endeavor to gain favor with researchers and to eschew behavior they fear might provoke retaliation.

While such environmental and psychological difficulties may make it virtually impossible to balance logically the advantages and disadvantages of participating in potentially hazardous research, concerns also arise that the dying, having abandoned all hope, may assent to immoral or unduly unwise experiments when experimenters exploit potential subjects' despair or incapacity. Oncologists, for example, justify employing countless approved drugs for unapproved uses with claims that they are simply responding to the desires of their dying patients. But as one physician to cancer patients remarks,

This argument abandons the scientific basis for medical practice and could just as well be used to justify quackery. Also, one wonders how many patients with advanced pancreatic cancer . . . would really demand cytotoxic drugs if the sheer futility of such therapy was honestly explained.<sup>66</sup>

Depression may likewise contribute to willingness to consent, rendering the significance of risk meaningless. Such a nothing to lose attitude among experimenters, however, proves most problematic: patients confronting imminent death are real people, not objects, who may treasure quality of life over its length. When a researcher deems a study useful or necessary, he may opt not to scrutinize the act of consent for fear of losing precious research resources.

Respect for autonomy *superficially* suggests that the desperately ill should be afforded considerable freedom to consent to experimental study participation. The terminally ill stress liberty to control one's body, a particularly acute concern when no alternative treatments to investigational therapy exist. Autonomy, however, is not absolute; drug regulation involves a dilemma between the competing concerns of scientific validation and individual choice. FDA thus faces the nettlesome task of weighing societal goals against each person's freedom, for every time access is broadened, science is jeopardized.<sup>67</sup> Patients willing to forego thorough

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<sup>67</sup> See Lois K. Perrin, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69 S. CAL. L. REV. 105, 153 (1995).

scientific validation of a treatment are denied access, yet selecting a course of treatment is an important consideration for the seriously ill. Traditional FDA policies require that a drug be proven safe and effective prior to distribution in interstate commerce and bar access to investigational therapies for noninvestigational ends. To respect autonomy more effectively, however, the Administration has allowed the sale of certain drugs still under investigation for AIDS patients and has promulgated regulations allowing marketing of drugs of unknown safety if benefits appear substantial. Such policies reduce the length of time necessary to test drugs for severely debilitating diseases, have revolutionized access to novel treatments for life-threatening diseases, and minimize differences between access to experimental drugs and to investigational procedures.

This vindication of autonomy, however, forces doctors as well as patients to render difficult decisions in the absence of substantial information. More troubling is that FDA's loosening of its drug approval procedures partially emanates from compassion toward those unable to survive long enough to wait for exhaustive testing of new therapies. Compassionate motivations can interfere with the furnishing of information and preclude straightforward conversations between patient and experimenter about the reasonable likelihood of success. They additionally may bury the character of an intervention and sacrifice the researcher's complete consideration of the project at hand. Most significantly, however, they further obscure the profound difference between the scientific alliance between researcher and subject and the therapeutic alliance between doctor and patient, rendering the distinct roles of each party to these relationships indistinguishable.<sup>68</sup> Just as the compassion argument proves flawed, scrutiny of experience with the drug AZT displays significant shortcomings of claims for greater access to experimental therapy premised upon autonomy and highlights the need for research performed in a systematic, scientific manner. AIDS is seen as an illness in which there is no distinction between experimentation and treatment since no cure exists. The disease overwhelmingly plagues the young, hastening a premature and certain death. Many afflicted thus are willing to disregard dangers

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<sup>68</sup>See Churchill et al., *supra* note 19, at 41.

associated with experimentation for even remotest chance of therapeutic gain. In the absence of alternatives, the importance of individual autonomy appears to supercede the government interest in safeguarding overall health. As AIDS activists clamored for increased access to experimental therapies, the public began to appreciate the tangible benefits research participants enjoy, including possible therapeutic advantages when other treatments prove ineffective, contact with eminent physicians, and careful monitoring of one's disease. Participation in clinical trials came to be regarded as a boon rather than a bane against which to be protected, further blurring the line between research and therapy. ACT-UP's slogan, A Drug Trial is Health Care Too, indeed encouraged AIDS victims to procure experimentation as treatment and researchers to deem AIDS patients potential subjects with nothing to lose. FDA bowed to pressures to expand access as well as to hasten new drug approvals, granting AZT fast-track treatment since initial studies suggested it was effective in combating AIDS.

Later evidence, however, demonstrated that this highly toxic substance with dire adverse effects cannot be tolerated by many patients and may furnish only fleeting benefits. Merely four of one hundred patients experience a slower progression of the disease,<sup>69</sup> meaning that FDA's allowance of greater access to AZT may have caused many to rely on a substance not nearly as efficacious as initially promised. If, as with AZT, patients pin hopes on the first drug to offer promise, they may sacrifice other innovations altogether. Absent a subject population to test the safety of alternative potential cures, new treatments cannot be established unless the initial treatment is clearly ineffective. The AIDS epidemic additionally evinces that the dangers of experimental drugs cannot be overemphasized: unofficial trials involving an ingredient known as Compound Q lacked safeguards such as an IRB and resulted in numerous fatalities.

The AZT story likewise demonstrates the difficulty of securing informed consent due to the blurring of the research/ therapy line. Terminally ill patients advised that medicine cannot offer them any hope come to re-

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<sup>69</sup> See Dominguez-Urban, *supra* note 13, at 259.

gard experimental protocols as treatment. Instead of approaching experimentation with skepticism, they may demand access to such interventions as a right; in such instances, informed consent affords no profound protection. Terminally ill research subjects commonly fail to comprehend that they are participating in research that may not be intended primarily for their benefit, a phenomenon termed the therapeutic misconception. Self-deception in viewing experimentation as treatment, particularly evident in terminally ill cancer patients, proves readily apparent in Phase I drug studies with anticancer agents. FDA regulations state that such investigations are not intended to possess any therapeutic content, yet the National Cancer Institute labels them potentially therapeutic.<sup>70</sup> Furthermore, nearly any intervention can be portrayed as potentially therapeutic, transforming nonbeneficial studies such as therapy. Deception enables researchers as well as subjects to double themselves, the former seeing themselves as physicians and the latter deeming themselves patients.<sup>72</sup> When the physician and researcher are embodied in the same person, it proves unlikely that patients can ever distinguish between these two conflicting roles, unable to fathom that their doctor would consciously employ them as a means for his own ends. Physician-investigators have long asserted that clinical research and therapy are inextricable, that drugs and therapies they scrutinize in scientific studies could be offered to patients in scientific settings, and that the sole distinction between their research and clinical endeavors lies in the objective evaluation of effectiveness and risk-benefits to which they submit their interventions.<sup>73</sup> Many likewise maintain that patients

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<sup>70</sup>See George J. Annas, *Questing for Grails: Duplicity, Betrayal, and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL'Y 297, 310-11 (1996).

<sup>71</sup>Eric Kodish et al., *Ethical Issues in Phase I Oncology Research: A Comparison of Investigators and Institutional Review Board Chairpersons*, 10 J. CLINICAL ONCOLOGY 1810, 1812 (1992), *quoted in id.* at 311.

<sup>72</sup>Another difficulty surrounding consent which AIDS and AZT highlight is the practice of administering placebos to a control group. One cannot help but question the ethical propriety of withholding the only potential treatment from terminally ill patients to acquire accurate data for future generations. In 1997, US-sponsored HIV research involving AZT in developing countries attracted considerable criticism since clinical trials involved placebo-controlled testing among pregnant HIV+ subjects. It is difficult to accept that patients will consent to participation in such studies if truly informed consent about risks and alternatives—namely that placebos offer no protection—occurs. Justifications for withholding information on placebos, including that the investigator does not know with certainty that placebo is inferior as well as that a patient will grow distressed if she learns she is being given a less desirable treatment, clearly undermine goals of promoting autonomy and informed choice.

<sup>73</sup>See Katz, *supra* note 33, at 12.

are exposed to unscientifically proven, ineffective, and potentially hazardous therapies in clinical practice, about which patients learn little since their doctor believes in these therapies and many other professionals share their physician's unsubstantiated beliefs. Clinical research, investigators posit, differs from therapy solely in that it seeks not to perpetuate scientific unknowns, but to resolve uncertainties. To the extent that patient-subjects assume that physician-researchers act in their best interests, then, informed consent constitutes little more than a fiction. For the terminally ill who do attempt to ponder the risks of research, their decision-making capacity is nevertheless impaired by the psychological and physiological effects of their sickness.

Our quest for a formula that will banish death seems to make it acceptable to try questionable regimens on the... terminally ill... Those who insist on using the dying as experimental subjects... see death as abnormal and dying patients as subhuman.<sup>74</sup> We must cease treating the terminally ill as subhuman by offering them dubious experiments under the guise of therapy. Such an offer cannot be justified by their demands for autonomy or by our belief that knowledge gained will benefit mankind. Researchers who believe their subjects have nothing to lose by participating in experimental studies should be disqualified from performing such research, for they are unable to protect the welfare of their subjects adequately. Similarly, subjects harboring the same sentiments and desperate due to their malady should be disallowed to participate since they cannot furnish competent, informed, and uncoerced consent.

Despite their nonmention in federal regulations, the terminally ill arguably constitute our most vulnerable population and need many more safeguards than currently provided. Not only should federal regulations explicitly classify the terminally ill as a vulnerable population, but research on this class should also be prohibited unless it potentially offers therapeutic benefits to individual subjects. Patients should receive confidential psychological evaluations prior to participation in studies, IRBs should be required to consult

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<sup>74</sup>Ralph Brauer, *The Promise That Failed*, N.Y. TIMES, August 28, 1988, sec. 6 (magazine) at 34, 76, *quoted in* Annas, *supra* note 34, at 134.

with a representative devoted to safeguarding their rights, researchers should be trained to recognize the psychological troubles plaguing those facing imminent death, and subject advocates should be available to assist the terminally ill during the informed consent process.<sup>75</sup> The terminally ill share several characteristics of other vulnerable populations: like children, their ability to make informed decisions is frequently impaired, and like prisoners, they are captives of their sickness, the hospital, and their doctor. Absent explicit regulatory classification of the terminally ill as vulnerable, numerous researchers and IRBs will disregard the susceptibility of the terminally ill. Even those scientists who appreciate vulnerability of their patients may not take adequate care to respond to the particular psychological trauma that a terminal diagnosis causes. Recognizing the fragility of the terminally ill would hardly impact the rapidity with which research is conducted and thus would not significantly lessen the societal benefits of such research. General regulations applicable to vulnerable populations are essentially unobtrusive for IRBs and researchers alike.<sup>76</sup> Categorizing the terminally ill as vulnerable likewise will not endanger their autonomy and dignity. Rather, it will demand they be regarded as complete individuals battling the psychological effects of their illnesses, but who are entitled to render their own informed decisions. Regardless of agreement with the aforementioned proposals on how to protect the terminally ill more effectively, one must concede that scrutiny of this class of subjects emphasizes that [i]nvariably, regulation of human research involves tradeoffs between the personal autonomy and rights of research subjects, potential benefits to society, and the need to prevent research abuse [and that] [r]easonable people... differ as to how this balance should be struck.<sup>77</sup>

### Women

Whereas the terminally ill suffer from underprotection, women have traditionally been disadvantageously

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<sup>75</sup>See Addicott, *supra* note 64, at 481.

<sup>76</sup>See *id.* at 510.

<sup>77</sup>*Id.* at 524.



overprotected and systematically excluded or underrepresented in clinical research studies. Because of their reproductive capabilities, women and their potential fetuses have been regarded as meriting safeguards from the possible hazards of experimentation. This policy of fetal protection, opines one author, results from intellectual lassitude, defensive legalism, and a misplaced sense of obligation.<sup>78</sup> Researchers routinely deem female subjects more vulnerable than male ones and assume that unvalidated treatments present unique reproductive hazards to all women. They frequently label pregnant individuals incapable of effectively weighing risks to a fetus against their own well-being and therefore deny these women the chance to participate in studies, regardless of the true level of risk involved. Research protocols typically ostracize nursing and pregnant women as well as females of childbearing age; the few that welcome pre-menopausal women strictly regulate their reproductive activities. Recent GAO investigations reveal that numerous clinical trials funded by the NIH were designed to include women, but not in numbers high enough to allow analysis that would definitively measure different outcomes for men and women.<sup>79</sup> The assumption that female physiology diverges from the norm has proven damaging in medical research, for it deems results accurate only for (white) men scientifically acceptable and thus perpetuates the practice of banning women from clinical trials for the sake of simplicity. Researchers often posit that the male body is less complex and that it is therefore easier to study men and generalize findings to women rather than to perform research on women directly. One study on links between obesity and breast as well as uterine cancer, for example, employed only male research subjects since experimenters believed their work could be performed more rapidly on nonmenstruating individuals. Another study on the effects of aspirin in reducing heart attack likewise involved twenty-thousand males yet no females. Desires to conduct studies with homogeneous populations and concomitant concerns

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<sup>78</sup>Jonathan D. Moreno, *Ethical Issues Related to the Inclusion of Women of Childbearing Age in Clinical Trials*, in WOMEN AND HEALTH RESEARCH (A. Mastroianni, R. Faden, D. Federman, eds., vol. 2, 1994) 29, *quoted in* Karen L. Baird, *The New NIH and FDA Medical Research Policies: Targeting Gender, Promoting Justice*, 24 J. HEALTH POL. POL'Y & L. 531, 532 (1999).

<sup>79</sup>Robert Pear, *Research Neglects Women, Studies Find*, N.Y. TIMES, April 30, 2000, at A16 (col. 4).

for cost-effectiveness repeatedly have been offered as justifications for passing over groups other than white men in medical research. Perceptions of the middle-aged male as the common breadwinner and stress on the economic costs of health care may also have contributed to overemphasis of concern on men's health. Researchers likewise label women unreliable, unlikely to follow through with research protocols because of child care demands or because they may become pregnant. As policymakers as well as researchers prioritize issues resounding with their personal concerns, it proves additionally problematic that in a scientific community which funds what it fears, women comprise a minority of medical researchers and a minute percentage of those making funding decisions.

These general rationales for excluding and underrepresenting women do not withstand scrutiny. It defies logical consistency to contend both that women are different from men due to their hormonal cycle as well as their ability to become pregnant and that females are similar enough to males to apply clinical research findings gleaned from studying the latter easily to them. Furthermore, the practice of generalizing findings to women undercuts their unique health care needs, for some illnesses manifest themselves differently or exclusively in women. An additional shortcoming of the protectionist rationale is that it assumes an adversarial relationship between a woman and her fetus, premised upon the belief that fetuses necessitate protection from their carriers. It consequently destroys a woman's right to control her pregnancy as well as her decision-making freedom.<sup>80</sup> Experimenters have long offered potential pregnancy, however remote, as a rationale for banishing all women from research protocols, yet automatic exclusion without substantiation of harm to the pregnant individual is unnecessary. Drop-out rates likewise can be factored into any study. More effective methods to achieve homogeneity, furthermore, exist; use of gender and race to obtain this end are simplistic, weak proxies. AIDS research, for example, reveals that accurate indices of homogeneity include defining a range of T-cell values or other virologic and hematologic abnormalities characteristically

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<sup>80</sup>See Hayley Gorenberg and Amanda White, *Off the Pedestal and Into the Arena: Toward Including Women in Experimental Protocols*, 19 N.Y.U. REV. L. & SOC. CHANGE 205, 210 (1992).

associated with the illness.<sup>81</sup> Such general exclusionary rationales may prove flawed, yet drug trial sponsors frequently cite possible exposure to tort liability as a rationale for eliminating women from trials. The primary source of concern lies in fear of potential damage to offspring, a result of the Thalidomide debacle of the 1950's in which thousands were born with birth defects and many stillbirths occurred.<sup>82</sup> The next decade saw discovery of complications of DES, which caused many daughters of women who had taken the drug to develop reproductive abnormalities as well as a heightened risk of vaginal cancer. Suits brought by these offspring proved costly to the pharmaceutical industry, provoking protectionist policies which in turn ironically hurt those intended to be safeguarded. Whatever liability risk exists in research, however, may be contained through informed consent. Judicial precedent demonstrates that without other negligence, informed consent acts as a shield against liability. Warnings, including disclosure of possible harms to the fetus, furnished during the informed consent process both maximize autonomous decisionmaking and minimize chances of recovery in tort actions for research injury. Additionally, the low incidence of such injury nearly eliminates likelihood of liability imposition.

Chances for liability are indeed minimal. The most notable instances of liability involving women as experimental subjects turned not upon effects on offspring, but upon failure to secure subjects' informed consent.<sup>83</sup> Only three reported cases implicate alleged research injuries to offspring resulting from clinical study participation, and in all instances, pregnant subjects did not consent to participate in research.<sup>84</sup> Such precedent thus does not delineate the boundaries of liability for harm to children when a woman has legally consented to participate in a clinical study. It additionally proves unclear whether securing a mother's consent

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<sup>81</sup>See *id.* at 214.

<sup>82</sup>These exclusionary policies prove misguided since they fail to address the root of the problem. The thalidomide crisis, for example, may have been averted through controlled, pre-marketing research. See *id.* at 208.

<sup>83</sup>See *id.* at 226.

<sup>84</sup>See Anna C. Mastroianni, *HIV, Women, and Access to Clinical Trials: Tort Liability and Lessons from DES*, 5 DUKE J. GENDER L. & POL'Y 167, 176 (1998).

suffices to eschew liability for injury to offspring, for an unborn child does not possess the capacity to consent. While one cannot deny that trials must be meticulously crafted with tort liability in mind, the search for a cure simply cannot exclude women.<sup>85</sup> Ironically, banishing women from clinical studies may in fact *expose* drug manufacturers to liability.<sup>86</sup> Liability for exclusion may occur when a woman takes a drug untested on her sex which proves more hazardous or less efficacious in females once marketed. Case law indicates that insufficient study constitutes grounds for imposing liability according to negligence and strict liability principles. Manufacturers face strict liability due to defective product design, and deficient testing may be deemed a design defect. Manufacturers likewise must warn about predictable risks that should be known, a requirement that can be met only with sophisticated product testing. Claims that a drug is unavoidably unsafe may be undercut if it is not tested on women but has damaging results, and liability can attach from lack of data requisite to determine appropriate protections for treatment of women. Clinical trial sponsors thus cannot eschew tort liability by omitting women in their childbearing years from protocols, rendering decisions to exclude these women from studies or to ignore the possibility that they may become pregnant while taking a marketed drug dangerous.<sup>87</sup> Depriving women of access to clinical research and treatment additionally fuels possible charges of gender discrimination, for the Supreme Court has fortified a woman's prerogative to make choices affecting reproductive status.<sup>88</sup> Recognition in UAW v. Johnson Controls, Inc.,<sup>89</sup> a Title VII

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<sup>85</sup>*Id.* at 191.

<sup>86</sup>Doctors may additionally incur liability for delivering treatments without informed consent since the possibilities for harm caused by drugs are unknown and patients do not anticipate being given untested medication or participating in de facto experiments when they visit their doctor. By excluding women from clinical trials, liability is not eliminated but instead passed from researchers to physicians, who become susceptible to malpractice suits for administering drugs with scarce knowledge of potential ramifications.

<sup>87</sup>Interestingly, drug manufacturers additionally court liability by failing to study possible male reproductive consequences of experimental drugs.

<sup>88</sup>See Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 HOUS. L. REV. 1201, 1242 (1996).

<sup>89</sup>499 U.S. 187 (1991).

challenge to a fetal protection workplace policy, that diverging applications of privileges to the sexes constitute gender discrimination and that choices affecting future children are rightly made by those who conceive and bear these children provides a foundation from which to attack differences in clinical research premised upon sex. Court rejection of fetal safeguarding bolsters the claim that prohibiting female participation in experiments for reproductive reasons is discrimination against women as women.<sup>90</sup> Possibility of liability for banning female trial participation again highlights an evolving view of participation in research as a benefit, if not a right, presenting nontrivial opportunities for direct medical gain.

Blanket exclusion of women from clinical trials must be labeled unconscionable because of the severe harm it works upon countless women. Physicians wishing to prescribe to female patients drugs untested on women are left to guess at appropriate dosages, possible side effects, and efficacy. Post-marketing studies of drugs are not required to secure drug licensing, meaning that women serve as marketplace guinea pigs, experimented upon by their doctors.<sup>91</sup> Furthermore, the virtual absence of female participants in medical research yields a general scarcity of information pertaining to women's medical care and consequently of knowledge crucial to their health and well-being. Doctors are sometimes slow to appreciate hazardous drug combinations for women- one example being the disproportionate occurrences of dangerous heart rhythm abnormalities that concomitant use of Seldane and erythromycin or ketoconazole causes - for a mere 15% of published research contains any analysis of the differences in results for women and men.<sup>92</sup> Knowledge of a drug's effects upon the expectant mother's unique physiology is likewise crucial for healthy pregnancies. Treatments that can save or extend her life, if endangered, may furnish the sole opportunity to protect the life of her fetus. The

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<sup>90</sup> See Rothenberg, *supra* note 88, at 1243.

<sup>91</sup> See Gorenberg and White, *supra* note 80, at 222.

<sup>92</sup> See Pear, *supra* note 79.

consent process affords the pregnant individual an opportunity to render informed, free decisions, thus promoting equality, autonomy, and self-determination in research as well as reducing manufacturers' likelihood of facing successful liability claims.

More fundamental, however, are the troubles emanating from employing the male body as a reference for judgments about the average individual. The practice renders the female experience of menstruation, hormonal cycles, and pregnancy exceptional rather than commonplace.<sup>93</sup> Disregarding material variables which entangle homogeneity may infiltrate studies with significant error, yet women desire and require accurate information about illnesses and conditions which afflict them. Such information can also promote women's health in general. As research enables us to enjoy healthier lives, and healthier individuals are better able to develop their capacities and talents, health can be regarded as none other than a first-order need.<sup>94</sup> The effect of the AIDS epidemic upon the female population also vividly illustrates the importance of gender-specific information. Failure to include adequate numbers of women in clinical studies of HIV and AIDS has detrimentally impacted the health of females suffering from the illness. When women have been at the center of AIDS research, it is usually to determine the most effective manner to bar or mitigate transmission of HIV to a fetus, rather than how to best treat gender-specific manifestations of HIV. It thus proves unsurprising that women suffered grave side effects when given AZT dosages calibrated to the 70-kg male. Furthermore, those who fit the Center for Disease Control's AIDS profile receive timely Social Security benefits, yet the CDC's definition of AIDS relies on symptoms present in men. Women suffering from HIV experience a variety of recurring gynecological disorders, including cervical cancer, pelvic inflammatory disease, and chronic yeast infections, yet the CDC definition does not reflect these symptoms.<sup>95</sup> Thus, many women with severe

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<sup>93</sup> See R. Alto Charo, *Protecting Us to Death: Women, Pregnancy, and Clinical Research Trials*, 38 ST. LOUIS U. L.J. 135, 142 (1993).

<sup>94</sup> See Baird, *supra* note 78, at 547-48.

<sup>95</sup> See Gorenberg and White, *supra* note 80, at 221.

HIV-related disabilities do not qualify for needed benefits; roughly 65% of females dying from HIV-related illness do not meet the CDC definition.<sup>96</sup> Women diagnosed with AIDS search in vain for treatments designed specifically to mitigate the disease's effects on the female body, causing females to be the fastest growing group of those dying from the illness. In light of the rapidity with which women aged twenty-five to forty-four- i.e. of childbearing age- are acquiring AIDS, it proves crucial that women not be denied the benefits of research.<sup>97</sup> Not only does exclusion deprive individual infected women of their sole chance to prolong life, but it also endangers the welfare of potential offspring.

Rectification of women's traditional exclusion from AIDS research as well other clinical trials additionally demands that special attention in the informed consent process be given to issues particular to women. If the basal goal of consent is to enhance self-determination of research subjects, disclosure of information as well as assessment of voluntariness cannot involve one monolithic standard. For women, experimenters must adopt a standard that accounts for stereotypes of women as incapable, less able, or untrustworthy decision-makers and that resists gender norms fostering female subordination. Women often defer to physician authority and do not wish to appear impolite. Older women are especially accustomed to paternalistic relationships with their physicians, while socioeconomically disadvantaged women as well as those of color may not view themselves as autonomous agents, thus reluctant to ask questions, voice concerns, or assert themselves.<sup>98</sup> Women of color are often viewed as poor decision-makers and thinkers: a physician asked about his failure to secure consent from Mexican-American women participants in a contraceptive study involving the possibility of receiving placebos replied, If you think you can explain a placebo test to women like these, you never met Mrs. Gomez from the West Side.<sup>99</sup> More generally, a Commonwealth Fund survey indicates that one in four

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<sup>96</sup> See *id.*

<sup>97</sup> See Mastroianni, *supra* note 84, at 170.

<sup>98</sup> See Lisa A. Eckenwiler, *Pursuing Reform in Clinical Research: Lessons from Women's Experience*, 27 J. L. MED. & ETHICS 158, 164 (1999).

<sup>99</sup> *Id.* at 160.

women report being talked down to or treated like a child by a physician, as compared with only 12% of men. Likewise, 17% of women have been told a medical condition was psychosomatic, whereas only 7% of men have been offered the same diagnosis.<sup>100</sup> A researcher seeking women's consent must recognize that they may fear coercion or ridicule and find participation problematic due to family responsibilities. Such matters must be addressed by NIH and FDA policies if medical research truly is to embrace women.

Recent NIH reforms resulting from the 1993 Revitalization Act have greatly ameliorated research policies pertaining to women. All applications for both intramural and extramural research must now include women as subjects. The Act additionally mandates that valid analysis be performed to demonstrate whether variables under scrutiny impact subpopulations and the sexes in varying ways. NIH guidelines state that:

[I]t is imperative to determine whether the intervention or therapy being studied affects women or men... differently. [These guidelines seek] to ensure that all future NIH-supported... research... will be carried out in a manner sufficient to elicit information about individuals of both genders and... to examine differential effects on such groups.<sup>101</sup>

The chief requirements for valid analysis are that allocation of women and men to the intervention as well as control groups occurs by a neutral process such as randomization, that researchers perform impartial evaluations of the results of studies, and that unbiased statistical methods be employed to gauge and compare intervention effects among the genders. NIH guidelines additionally delineate when women may and may not be prohibited from participating: cost is not an acceptable justification, and exclusion cannot be substantiated unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant

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<sup>100</sup>See THE COMMONWEALTH FUND SURVEY OF WOMEN'S HEALTH (The Commonwealth Fund, New York 1993) pagination not available, *quoted in* Baird, *supra* note 78, at 552.

<sup>101</sup>U.S. DEP'T OF HEALTH & HUM. SERVICES, NAT'L INST. HEALTH, 1994a *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*, FED. REG. 59(59):14508, *quoted in* Baird, *supra* note 78, at 549.



institute...that the inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.<sup>102</sup>A trial may include only one sex if the disease or disorder being studied is gender-specific; in all other instances, experimenters are to use roughly equal numbers of men and women. Such an approach promotes gender justice, striving to furnish women with beneficial medical knowledge and aiding them in enjoying healthier lives. The 1993 reforms likewise demand that a data system for collection, retrieval, and dissipation of knowledge on women's health research which NIH supports be established.

NIH publication of an Outreach Notebook to aid scientists in complying effectively with new guidelines also deserves commendation, for it offers tips on how to include women as well as on recruitment tactics. Guidelines recommend

establish[ing] a relationship...[which] represent[s] a thoughtful and culturally sensitive plan of outreach and generally include[s] involvement of other individuals and organizations relevant to the populations and communities of interest...The objective is to establish appropriate lines of communication and cooperation to build mutual trust and cooperation such that both the study and the participants benefit from such collaboration.<sup>103</sup>

The Notebook warns researchers that issues of coercion prove especially important in dealing with female subjects. Attention to cultural concerns as well as to the importance of establishing mutual trust additionally evince respect for women and will work to mitigate many of their reservations concerning protocol participation. NIH recommendations likewise stress that researchers should exert special effort to ensure that women are fully informed and issue free consent. They also alert researchers to constraints such as child care, which may affect the ease with which women of differing ages and socioeconomic statuses can participate. Such concerns explicitly acknowledge and legitimize women's experiences,<sup>104</sup>previously unrecognized

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<sup>102</sup>*Id.*, quoted in Baird, *supra* note 78, at 550.

<sup>104</sup>*See* Baird, *supra* note 78, at 553.

or used to justify female exclusion. NIH regulations have been written into law, and the Departments will no longer fund any projects failing to comply with new policies on the inclusion of women. Researchers, furthermore, must report yearly on gender of enrolled study subjects. While such advances bode well for the future, a recent New York Times article discouragingly reports that medical researchers who secure federal dollars now generally include women as subjects yet disregard the requirement to analyze the effects of novel drugs on them.<sup>105</sup> While NIH has moved from encouragement to requirement with respect to female clinical trial participation, FDA has merely moved from banishment to encouragement. 1977 guidelines provided that pregnant women or those at risk for becoming pregnant should be excluded from Phase I studies and further exhorted that those of childbearing potential be banned from large-scale clinical trials until FDA animal reproduction tests were performed. Only if sufficient information on the effectiveness and safety were amassed during Phase II could women of childbearing potential, defined to include those using contraception, lesbians, celibate individuals, and wives whose partners had been vasectomized, be included in further protocols. FDA too issued new guidelines in 1993, stating that subjects in a clinical trial should reflect the population that will use the drug once marketed and suggesting that subjects include men as well as women to allow for comparative analysis.

The new guidelines, however, do not require that women be included in early drug trial phases. They demand that scientists secure informed consent from women, warn participants to take necessary measures to prevent fetal exposure to potentially hazardous drugs, and furnish information about risks of fetal toxicity. Nevertheless, guidelines still maintain that large-scale exposure of women of childbearing potential should not occur until results of animal toxicity tests are scrutinized.<sup>106</sup> FDA regulations additionally contain provisions hindering the ability to render changes in drug research procedures: these *hortatory* guidelines, which

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<sup>105</sup>See Pear, *supra* note 79.

<sup>106</sup>See Baird, *supra* note 78, at 540.

state that the Administration sees no need to mandate that women be included in specific trials, do not necessarily affect drug approval. Mention of the need for more extensive research in drugs and devices that might particularly benefit women is absent, as are details as to what comprises sufficient representation of women in protocols. FDA offers no counterpart to NIH's recognition of women's health experiences, ignores problems of drawing women to research participation, and fails to extend outreach programs to aid scientists in including females.<sup>107</sup> The Administration does, however, alter its former policy of eliminating women of childbearing potential from studies, reasoning that determinations of fetal risk are properly left to patients, physicians, local IRBs, and sponsors. . . .<sup>108</sup> This appreciation of women's competence to issue informed consent is a noteworthy improvement, though undue emphasis is still placed upon the fetus.

### Children

FDA policies have not safeguarded children adequately; while no drug can be approved prior to extensive tests in adults, drugs administered to children are approved regularly without pediatric testing. Over two-thirds of drugs sanctioned for use in the United States have not been tested in children,<sup>109</sup> despite the fact that many of these substances are regularly prescribed to them. Studies indeed indicate that merely 42% of drugs frequently used to treat children have been tested on pediatric subjects in clinical trials.<sup>110</sup> FDA perpetuates this situation with its Pediatric Use regulation, permitting manufacturers to escape pediatric testing in cases where the drug will not be marketed specifically for children if they affix a warning on the drug's label stating that [s]afety and effectiveness in pediatric patients have not been established.<sup>111</sup> As

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<sup>107</sup> See *id.* at 554.

<sup>108</sup> U.S. DEPT. OF HEALTH AND HUMAN SERVICES, FOOD & DRUG ADMIN., 1993. *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*. FED. REG. 58 (139): 39408, quoted in Baird, *supra* note 78, at 556.

<sup>109</sup> See Althea Gregory, *Denying Protection to Those Most in Need: The FDA's Unconstitutional Treatment of Children*, 8 ALB. L.J. SCI. & TECH. 121, 122 (1997).

<sup>110</sup> See Barbara A. Noah, *Racial Disparities in the Delivery of Health Care*, 35 SAN DIEGO L. REV. 135, 152 n. 63 (1998).

<sup>111</sup> 21 C.F.R. §201.57(f)(9)(vi)(1997).

FDA regulates drug manufacturers rather than physicians, doctors are free to prescribe drugs to youngsters despite the fact that they have not been tested in children. Likewise, no requirement exists that a physician secure informed consent for off-label use of drugs, meaning that children are left to the whims of physicians' discretion to advise them or their parents that they are receiving substances whose pediatric efficacy remains uncertain.

Dearth of testing in children proves significant since youngsters, whose physiology differs immensely from their seniors, do not absorb drugs in a manner identical to adults. Doctors may thus prescribe drugs in inappropriate dosages or may opt not to prescribe potentially beneficial yet untested drugs at all. While FDA may argue that pediatric testing will nevertheless occur as a result of market forces, minute market size and lack of profitability of adding a pediatric use to a drug label do not motivate drug manufacturers to alter current practices.<sup>112</sup> It should be noted, however, that FDA recently proposed to require manufacturers to collect and record pediatric data.

The proposal, though, prompts consideration of unique difficulties of informed consent which arise with children. Surrogate consent is necessary for protocols involving children. That of both parents is required where research implicates a greater than minimal risk with no chance of direct benefit to the individual child but proves likely to produce general knowledge of the subject's illness. Both parents must also consent if experimentation is not otherwise authorizable yet presents an opportunity to understand or mitigate a grave health problem affecting children. Youngsters themselves generally must assent to participation, yet regulations appear to bestow unrestrained authority to consent to their child's participation in research upon parents of small children unable to assent.<sup>113</sup> Parents, however, may be unable to isolate and safeguard an individual child's safety and dignity. In the Baby Fae case, for example, a dying child received an experimen-

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<sup>112</sup>See Gregory, *supra* note 109, at 146-47.

<sup>113</sup>See Holmes-Farley and Grodin, *supra* note 11, at 161.

tal baboon heart transplant. While the patient's mother consented, the procedure stands as a disheartening instance of a mother swayed by her child's forlorn situation. Even if consent was voluntarily and consciously given, it should never have been requested.<sup>114</sup> Surrogate consent proves nettlesome because one can never ascertain with certainty if the parent's decision is proper, i.e. loyal to the child's best interests and desires, if known. Those lacking capability to consent should not be coerced into altruism by way of their surrogates' choices, and proxy consent, which fosters an image of a powerless research subject, amounts to little more than a contradiction if consent seeks to exalt self-autonomy and self-determination. Willingness to accept proxy consent reflects our dilemma between devotion to individual dignity and utilitarianism: when forced to compromise the former to permit needed experimental procedures and trials, we hide the tradeoff and profess enduring respect for the value which was subordinated.<sup>115</sup> Prisoners

Concerns for human dignity and capacity to consent underlie the severe regulatory restrictions on conducting research on prisoners, ideal subjects not only for cost control reasons but also since life is subject to few variations. . . [and] [t]he imposition of experimental procedures that might inconvenience free. . . subjects is not a burden on [them].<sup>116</sup> Prisoners comprise a vulnerable population as a physically healthy, captive group ideal for studies necessitating constant monitoring of subjects as well as rigorous control over diet and activity. As demonstrated by the oft-cited prison research case of Kaimowitz v. MI Dept. of Mental Health,<sup>117</sup> prisoners may grapple with constraints due to their incarceration which impact their capacity to render truly uncoerced and free consent. The Michigan Circuit Court confronted a situation in which the patient had signed a consent form permitting experimental psychosurgery, and two committees had reviewed the consent process

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<sup>114</sup>See Garnett, *supra* note 6, at 486.

<sup>115</sup>See *id.* at 487.

<sup>116</sup>GEORGE J. ANNAS ET AL., INFORMED CONSENT TO HUMAN EXPERIMENTATION: THE SUBJECT'S DILEMMA (1977) at 103, *quoted in id.* at 478.

<sup>117</sup>Civil No. 73-19434-AW (Mich. Cir. Ct. Wayne County, July 10, 1973).

as well as the study. Holding that the procedure could not be performed even with the prisoner's consent, the Court judged the consent suspect partially due to the inherently coercive atmosphere of the institution.<sup>118</sup> It additionally commented on the precariousness of psychosurgery, adamant that psychosurgery should never be undertaken upon involuntarily committed populations, when there is a high-risk low-benefits ratio and raised concerns about bargaining power imbalances in the prison scenario.<sup>119</sup> Situational coercion proves problematic since it constrains the prisoner's freedom to render choices.

Compounding such difficulties is the message of the penal system- one which may be offered to exonerate experimentation- that prisoners necessitate reform and reshaping.<sup>120</sup> If prisoners regard themselves as requiring alteration, they may judge a hazardous reformatory experimental procedure in their best interests. One commentator notes, however, that the applicability of ethical principles should not depend on the participants' willingness... to take particular risks any more than a person's agreement to be a slave justifies slavery.<sup>121</sup> Although regulations require that incarcerated persons be clearly informed that participation will not impact parole opportunities, concerns nevertheless remain that prisoner motivation to consent may emanate from the hope of appearing more favorably before a parole board.

Prisoners are additionally protected in the regulations through explicitly prohibited inducements. Their participation may not be secured through advantages in living conditions or chances to accumulate earnings to a degree that would interfere with their ability to weigh the risks of research against the value of such advantages in the limited choice environment of the prison.<sup>122</sup> Holmesburg Prison studies which University of

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<sup>118</sup>Id., pagination not available, *quoted in* King and Henderson, *supra* note 4, at 1042.

<sup>119</sup>Id., *quoted in* Garnett, *supra* note 6, at 482.

<sup>120</sup>See Garnett, *supra* note 6, at 481.

<sup>121</sup>Wendy K. Mariner, *AIDS Research and the Nuremberg Code*, in NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 286-304 (George J. Annas and Michael A. Grodin, eds., 1992) at 295, *quoted in id.* at 493.

<sup>122</sup>45 C.F.R. §46.305(a)(2).

Pennsylvania scientist Albert Kligman performed demonstrate problems of inducement confronting prisoners. Tests involving prisoners helped formulate Retin-A skin cream, yet former inmates complain that they were not informed of possible long-term effects of the trials and were exploited and lured into participation through pecuniary means. One explains:

People coming from a street background making 75 cents an hour (on) a day job, going to jail and being able to make \$15 on a study [will participate]—that would give you commissary for

three weeks.<sup>123</sup> Guidelines for research involving prisoners do not merit criticism, however, because they place significant restrictions on the use of a vulnerable population in research yet afford the group the right to participate. For research implicating incarcerated individuals, IRBs may approve protocols only if researchers offer no questionable incentives to participate, dangers of participation would be acceptable to a free volunteer, pertinent information is furnished in understandable language, subjects are selected equitably, and prisoner participation does not bear upon parole decisions.<sup>124</sup> A majority of IRB members must also lack ties to the prison from which human subjects are drawn, and at least one member must include a prisoner or prisoner representative with applicable background knowledge and experience.<sup>125</sup> While regulations do not fully eradicate coercive forces present in prisoner decisionmaking, they greatly abate them without forcing IRBs to forbid prisoner enrollment in research studies. Foregoing such blanket exclusion proves extremely significant as the prison population includes large numbers of AIDS sufferers. Depriving them of the opportunity to participate in HIV-related protocols would deny them any chance to receive treatment, demonstrating that the sole equitable approach with respect to experimentation in vulnerable populations

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<sup>123</sup> *Ex-Inmates Seek Treatment for Prison Experiments*, (November 8, 1998) <<http://www.cnn.com/US/9811/08/acres.of.skin>>.

<sup>124</sup> See 45 C.F.R. §46.305(a).

<sup>125</sup> See 45 C.F.R. §46.304.

may be to permit participation.

### The Cognitively Impaired

Protecting the decisionally impaired presents a persistent definitional dilemma. Every individual may be labeled decisionally impaired at some moment due to causes such as disease, immaturity, traumatic life events, or side effects of medication. The term mentally disabled remains undefined in federal regulations, and it seemingly includes a vast array of conditions. For decisionally impaired persons, reduced decision-making abilities resulting from illness involving cognitive impairment and/or the captivity of institutionalization may create vulnerability. Similar concerns exist in elderly patients suffering from dementia, depression, and other psychoses frequently seen in life's advanced stages. Research on those manifesting such problems poses ethical complications, for psychiatric illness as well as dementing disorders impact or eradicate a subject's capacity to furnish valid informed consent. The precise relationship between possessing sound mind and ability to issue voluntary, informed consent plagues psychiatrists, judges, and attorneys,<sup>126</sup> as does the concomitant problem of safeguarding these vulnerable individuals while improving and making treatments for ravaging illnesses available.

Federal regulations, however, furnish no guidance on identifying or evaluating decisional capacity for purposes of participation in experimental protocols. Determination that a potential subject proves unable to consent to participation means that such consent must come from a surrogate or proxy, yet regulations offer scant guidance on this issue. Due to the absence of regulatory guidance as well as governmental resolve to address ethical issues pertaining to cognitively impaired research subjects, numerous organizations have promulgated and adopted research guidelines in the area. These guidelines put forth several sliding scales of permissibility and safeguards premised on categorization of protocols in terms of degree of risk as well

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<sup>126</sup>See Ruth Macklin, *Some Problems in Gaining Informed Consent from Psychiatric Patients*, 31 EMORY L.J. 345, 348 (1982).



as potential for direct, tangible benefit to the individual subject.<sup>127</sup> Lack of specific federal direction on research with decisionally impaired individuals has additionally meant that non-federally funded protocols have evolved in fifty different directions: state regulation in this area can be described only as a crazy quilt. . . with most [states] having no rules that clearly apply to this group while some are quite restrictive.<sup>128</sup> The decision in T.D. v. N.Y.S. Office of Mental Health,<sup>129</sup> for example, bans all state-sponsored research involving mental patients implicating greater than minimal risk and denying subjects potential benefits. This result foreclosed significant research on mental illness, namely department of psychiatry studies at Cornell, an institution possessing a vast portfolio of foundation-funded experiments. Clinical studies with decisionally impaired individuals must continue; performing it without undercutting the very humanity it aspires to promote will always demand a delicate balance.<sup>130</sup> If excessive protections are imposed on research participation of the cognitively impaired individual, they will disproportionately single him out and aggravate already existing stigmas. They will additionally deny the cognitively impaired individuals the equity and fairness afforded to other groups. Among subclasses of potential participants often regarded as vulnerable and necessitating stringent protection, the decisionally impaired are unique in that no federal regulations addressing them exist. Guidelines, however, are badly needed so researchers can more easily balance goals of advancing knowledge with safeguarding the welfare of human subjects.

The complications psychiatric patients present in securing informed consent further evince the need for such regulations. Federal guidelines mandate disclosure of any appropriate alternative courses of treatment which might benefit the subject, presenting fundamental hardships. Not only do a greater number of therapies with

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<sup>127</sup>See Marshall B. Kapp, *Decisional Capacity, Older Human Research Subjects, and IRBs: Beyond Forms and Guidelines*, 9 STAN. L. & POL'Y REV. 359, 361 (1998).

<sup>128</sup>Moreno, *supra* note 14, at 14.

<sup>129</sup>650 N.Y.S. 2d 173, 193-94 (N.Y. App. Div. 1996), appeal dismissed by 680 N.E. 2d. (N.Y. 1997); leave to appeal granted by 684 N.E. 2d 281 (N.Y. 1997), and appeal dismissed by 1997 WL 785461 (N.Y. Dec.. 22, 1997).

<sup>130</sup>See Moreno, *supra* note 14, at 20.

lesser degrees of certainty about effectiveness exist in psychiatry than in somatic medicine, but psychiatrists also often display adamant commitment to a particular mode of therapy.<sup>131</sup> These doctors thus may hesitate to outline alternative therapy possibilities to patients. Additionally, the therapy-patient relationship often is more germane to the progress and outcome of psychiatric treatment than is the physician-patient relationship to healing.<sup>132</sup> The trust and confidence a psychiatric patient places in his doctor proves a crucial component of the therapeutic relationship, especially where the patient's capacity to verbalize his thoughts is a significant part of the treatment. It is thus plausible for psychiatrists to reason that discussion of alternative modes of therapy might dilute the esteem a patient holds in his therapist, thereby interfering with the therapeutic process.<sup>133</sup> An additional obstacle to securing truly informed consent from psychiatric patients is the subject's ability to grant it. Questions of competence need not be raised for the large numbers of patients seeking psychotherapy for issues such as marital discontent, and incompetence may be recognized easily in cases involving patients unable to communicate, but most psychiatric cases lie in between these two extremes. As with prisoners, concern about voluntariness of consent arises with institutionalized patients. Various inherent characteristics of psychiatric patients, such as dependency, complicate the question of free consent to a proposed therapy or protocol. This complication is exacerbated by the fact that psychiatrists often possess the capacity to sway patients to consent to nearly anything.

Dealing with subjects whose decision-making capacities may be impaired is also a concern for investigators recruiting geriatric subjects, for this involves conducting research on individuals suffering from depression, dementia, or other late life psychoses. Safeguarding the elderly who are cognitively challenged and confined to hospitals or nursing homes is only one regulation mandating that a scientist procure legally effective in-

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<sup>131</sup> See Macklin, *supra* note 126, at 351-52.

<sup>132</sup> See *id.* at 352.

<sup>133</sup> See *id.*

formed consent of . . . the subject's legally authorized representative.<sup>134</sup> Effective trials and experiments must have older participants currently afflicted with a medical condition under scrutiny, yet as with other vulnerable populations, these subjects lack sufficient capacity to grant ethically valid consent to participate. Standards and procedures for capacity evaluation should reflect an appreciation that potential subjects need individual evaluation.<sup>135</sup> Requiring IRBs to involve independent third parties to succor and supervise consent negotiations involving the cognitively impaired elderly would improve the current situation.

While greater uniformity and specificity is needed in regulations pertaining to research involving all cognitively impaired classes, focus upon the knowledge and standardized tools requisite to measure ability to furnish consent to research participation also proves necessary. Evaluation to Sign Consent (ESC) is one test that has been developed to determine capacity to consent in clinical settings. A five-item questionnaire scrutinizing a subject's factual understanding of information pertinent to participation in a specific study, ESC could be employed to ascertain which patients possess sufficient capacity to grant ethically and legally valid consent. In the test's first systematic application to a randomized, clinical drug trial, sixteen of twenty-four subjects failed the assessment.<sup>136</sup> In contrast to ESC, which is a short and concrete aid inquiring only about study-specific facts, another standardized measure known as the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) involves a twenty-page questionnaire posing questions related to a hypothetical study. This long and abstract measure examines the effectiveness of the standardized assessment tool utilized to evaluate capacity to grant consent. While it may set an unreasonably high standard for psychiatric subject participation, the ESC test may not be sufficiently exacting.<sup>137</sup> These are the only

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<sup>134</sup>45 C.F.R. §46.116 (1992).

<sup>135</sup>See Kapp, *supra* note 127, at 362.

<sup>136</sup>See DeRenzo et al., *supra* note 37, at 83 (1998).

<sup>137</sup>See *id.* at 85.

two existing assessments of capacity-to-give-consent research tools in the testing phase,<sup>138</sup> yet both possess shortcomings. Further research pertaining to methods of assessing capacity to consent is thus in order.

#### Consent Complications in Modern Science: The Problem of Gene Therapy

Newer, more severe challenges to informed consent and vulnerability of subjects come with gene therapy. Genetic research proves likely to have an incredibly profound influence upon the twenty-first century, and the Human Genome Project already has impacted the direction of future research. The Project, which has seen recent successes in identifying and sequencing all sets of genes that comprise the human being, is expected to enable the curing of disease through information contained in genomic mapping. Investigators' hope that the Project will spur a therapeutic revolution has resulted in extensive promotion of human gene transfer research as therapy. The thorny ethical and legal dilemmas this practice raises, however, escalate with each new discovery.

Perhaps no event in recent human history has done more to highlight the results of deficient oversight than Jesse Gelsinger's demise. Pressured by Congress to explain flaws in gene therapy oversight, federal health officials conceded that they could not determine whether experiments had hastened or possibly caused the deaths of other subjects.<sup>139</sup> Subsequent to an NIH reminder, issued in the wake of the Gelsinger tragedy, to report all adverse occurrences related to gene therapy trials, 652 new problems surfaced, ranging from fevers to partial paralysis and death.<sup>140</sup> While admitting that it failed to report immediately three deaths to a governmental research agency, Boston's Beth Israel Medical Center stressed that it did inform FDA yet received no reply. Researchers at Boston's St. Elizabeth's Medical Center likewise failed to report the

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<sup>138</sup> See *id.* at 84.

<sup>139</sup> See Sheryl Gay Stolberg, *Senators Press for Answers on Gene Trials*, N.Y. TIMES, February 3, 2000, at A25 (col. 1).

<sup>140</sup> See Rachel K. Sobel, *Add Insult to Injury: Gene Therapy's Travails*, U.S. NEWS & WORLD REP., February 21, 2000, at 55.

death of a patient involved in a gene therapy experiment that may have contributed to the development of cancer in another patient. That latter subject's condition was also improperly reported. As discussion arose as to why investigators habitually flout federal guidelines to report experimental side effects in patients to NIH, one explanation surfaced: the Recombinant DNA Advisory Committee, its panel supervising gene therapy, lost authority to approve research protocols in 1996. As a result, scientists ceased to take the body seriously. Researchers additionally claim confusion surrounds which governmental agency should receive adverse reports, with NIH blaming FDA and FDA blaming NIH.

Recognizing that improvements in reporting are requisite if the public is not to remain skeptical, FDA and NIH announced an initiative in March, 2000 with potential to impact review of gene transfer trials profoundly. FDA will demand that sponsors of gene transfer trials regularly submit monitoring plans to it, and the Administration will review the plans, demand alterations where necessary, and supervise as well as inspect trials to certify proper monitoring. While these policies represent a significant response to misgivings over gene therapy trial oversight, they fail to address a large majority of clinical trials. Many trials occur outside the gene therapy context, and patients in them face tremendous risk.<sup>141</sup> Innovative research in genetics additionally illustrates that traditional solutions to consent have grown obsolete. With DNA banking, for example, disclosure of information involving the manner of safeguarding privacy, duration of time for which tissues will be stored, and whether biological material will be used for secondary research all need to be addressed if a subject's assent to participation is to be truly informed and voluntary.

Gene therapy also raises a difficulty present in clinical trials involving terminally ill subjects, namely the conflation of the research/ therapy distinction. NIH director Harold Varmus explains one factor contributing to the obfuscation:

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<sup>141</sup> See DEP'T OF HEALTH & HUM. SERVICES, OFF. OF THE INSPECTOR GEN., PROTECTING HUMAN RESEARCH SUBJECTS: STATUS OF RECOMMENDATIONS, OEI-01-97-00197 (April 2000) <<http://oig.hhs.gov/oei/reports/a447.pdf>>.

Expectations of current gene therapy have been oversold. Overzealous representation of clinical gene therapy has obscured the exploratory nature of the initial studies, colored the manner in which findings are portrayed. . . and led to the widely held, but mistaken, perception that clinical gene therapy is already highly

successful.<sup>142</sup> A March, 1996 report of the General Accounting Office additionally concedes that the line differentiating research from treatment is frequently nebulous to clinicians.<sup>143</sup> Conducting gene transfer studies in the context of patient care thus creates considerable confusion, with the blurring of research and therapy exemplified in the term gene therapy. The term both signifies novel insights into the workings of the human body and connotes routine therapeutic practice.<sup>144</sup> While the former meaning infuses gene therapy with appeal, the latter interpretation permits experimental interventions to be prematurely applied clinically as merely another therapeutic modality.<sup>145</sup> Another challenge to informed consent and human subject protection in the context of gene therapy involves physicians' financial incentives to perform experimental studies, which create conflicts of interest. Investigators have become increasingly involved in post-marketing research, prompting concerns that patient may receive scanty disclosure and that doctors possess sufficient motivation to sacrifice the interests of patient-subjects to their own fiscal ends. Concerns that biotechnology funds alter informed consent prove substantial: at University of Pennsylvania, the doctor directing the school's Institute for Human Gene Therapy at the time of the Gelsinger incident also founded a biotechnology firm in which he holds stock. This company provided him with the monetary backing for the Institute. Many researchers in the gene therapy have significant financial stakes in the field; the doctor overseeing the aforementioned

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<sup>142</sup>S.H. Orkin and A.G. Motulsky, NIH AD HOC COMM. REP., REPORT AND RECOMMENDATIONS OF THE PANEL TO ASSESS THE NIH INVESTMENT IN RESEARCH ON GENE THERAPY, October 7, 1995, *quoted in* Churchill et al., *supra* note 19, at 38.

<sup>143</sup>*See* GEN. ACCT. OFF., SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS, March 8, 1996, at 23.

<sup>144</sup>*See* Churchill et al., *supra* note 19, at 43.

<sup>145</sup>*See id.*

St. Elizabeth trials likewise is a founder of a company leading the trials and a major stockholder in it. Such involvement leads to doubts that clinical researchers enjoying equity in companies and who stand to gain from genetic experimentation can be trusted to report serious adverse effects occurring during such studies and to safeguard patient welfare. Harvard Medical School harbors this concern, prohibiting scientists with nontrivial financial interests in companies to participate in clinical trials of their products.<sup>146</sup>The St. Elizabeth's case demonstrates what may occur when such policies are absent: necessary tests were not performed in certain cases, several patients enrolled might not have been eligible for the study, and one included patient unquestionably should have been excluded under the experiment's rules.

Such flagrant errors result from rigorous competition for patients. Pharmaceutical companies typically need roughly 4000 subjects to test an experimental drug and pay physicians up to \$2500 per patient recruited.<sup>147</sup>Marketplace ideology now pervades medicine, placing considerable emphasis on profit. This mentality subordinates both scientific truth and patient welfare. One observer of new biotechnology laments that [t]o do science, you need money, but to raise money competitively you need to project illusions that are the antithesis of science.<sup>148</sup> Academic research itself is highly competitive, with researchers vying for lab space, grants, and top graduate students. Rewards for innovative research come in the forms of tenure, promotion, and opportunities at eminent universities and research sites. These considerations combine with financial incentives to foster a permissive attitude toward use of human subjects in which informed consent as well as patient autonomy is undervalued and the niceties of disclosure and consent are overlooked.<sup>149</sup>Scientists seek breakthroughs since continued financial support directly depends on demonstrated progress. This creates in-

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<sup>146</sup>See Richard A. Knox, *Physicians Deny Deaths Unreported: Researchers Dispute NIH Officials' Claim*, BOSTON GLOBE, November 4, 1999, at C1.

<sup>147</sup>See *Clinical Trials Database Goes Online*, N.Y. TIMES, February 28, 2000, at A14 (col.4).

<sup>148</sup>Barry Werth, THE BILLION DOLLAR MOLECULE 355 (1994), *quoted in* Annas, *supra* note 70, at 317.

<sup>149</sup>Delgado and Leskovic, *supra* note 29, at 104.

centives to inflate claims regarding the therapeutic hope new interventions may offer. Despite the significant financial and reputational motivations of investigators, IRBs as well as individual subjects regularly possess no knowledge of the ways in which these factors influence the applicable researcher. While financing has been the most tangible, significant change in clinical trials over past decades, it remains unaddressed in federal regulations. Regulatory reform is needed to prevent monetary considerations from demoting autonomy and subject safety as well as from bolstering therapeutic misconceptions.

#### Proposals for Future Improvement in Informed Consent and IRBs

Problems of informed consent in gene therapy and in research generally evince that more care must be taken in divorcing clinical trials from therapy and that more meaningful conversations between investigators and potential subjects must take place. Physician-researchers must regard themselves as scientists only, not as doctors, for they become double agents with conflicting loyalties by conflating research with therapy and subjects with patients.<sup>150</sup> Legally sufficient consent may not be morally valid, however, because morally valid consent seeks true con-sent, an agreeing together.<sup>151</sup> A rigorous, clear policy mandating full disclosure could promote autonomy by creating an awareness in patients not to trust physicians to restore health, but rather to rely on an experimental protocol to produce valuable knowledge and perhaps ameliorate their condition. To secure truly valid consent, researchers should be required to explain: (1) that subjects are not only patients, and to the extent to which they are patients, their therapeutic needs will be subordinated to scientific concerns; (2) that a research protocol and question guide the experimental study, and individual interests will be subordinated to scientific concerns; (3) that clinical research seeks to furnish doctors with information on which treatments are most hazardous, beneficial, or ineffective; (4) that clinical research may be in the subject's immediate best interest, future interest, or may offer no benefit at all, especially if the patient

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<sup>150</sup>See Katz, *supra* note 33, at 28.

<sup>151</sup>See *id.* at 34.



receives a placebo; (5) that it is uncertain if the patient's welfare would be promoted through treatment by a physician rather than a doctor-investigator; and (6) that the researcher will respect whatever decision the subject ultimately makes.<sup>152</sup> Additionally, informed consent should be deemed an ongoing process in which preliminary data the study yields is furnished to subjects, who are assured of continual receipt of information when they initially consent to participate. Conversing forthrightly with patients will afford them a more profound understanding of the difference between clinical research and therapy.

Informed consent is fundamentally about language and communication between subjects and researchers as well as physicians and patients, yet the process currently does not promote candor. Attention thus should be given to meaningful communication rather than to supplying mere facts. Doctors enjoy the best position to foster discussions since subjects and patients may not possess enough information even to formulate questions or voice reservations. The medical profession must come to recognize that patients desire substantial disclosure on dangers and alternatives to a particular procedure or study both to decide upon a the most appropriate course of treatment and to know what to expect. On the other hand, subjects should no longer be barraged with esoteric medical information that elucidates little and obfuscates basic, crucial facts needed to issue informed and voluntary consent. Researchers thus bear an obligation to translate scientific jargon into language comprehensible and pertinent to subjects and to purge informed consent forms of distracting, inconsequential technical information.<sup>153</sup> Consent forms thus require meaningful alteration, for they currently provide a better understanding of an investigator's aims to IRBs rather than to potential subjects. Gene transfer research consent forms, for example, should plainly indicate that no expected benefit to the individual subject exists. As George Annas observes,

[W]e must use language to clarify rather than obscure what we

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<sup>152</sup>See *id.*

<sup>153</sup>See *id.* at 36.

do to one another. Minimally, we must correctly identify and describe roles and responsibilities in human experimentation. . .

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t may not be realistic to think we can always distinguish research from therapy, physicians from scientists, or subjects from patients. Nonetheless, it's morally imperative to use language to clarify. . . .because ignoring these differences undermines the integrity of scientific research, the integrity of the medical profes-

sion, and the rights and welfare of subjects and patients.<sup>154</sup> Candor additionally suggests that federal regulations must require researchers to reveal any and all fiscal incentives involved in experimentation to potential subjects as well as to IRBs. Guidelines might also be amended to condition federal funding on the premise that no institutional employee may enjoy a personal financial incentive in research. Additionally, they might require that any profits from research be deposited in university research accounts and utilized for the good of persons similar to the subject or to promote study into the condition examined in the protocol.<sup>155</sup> Such mandates would extend academic conflict rules existing at many state and local institutions to research settings nationally, promoting greater uniformity.

Informed consent could further uplift autonomy through adoption of a life plan approach.<sup>156</sup> Researchers would be required to determine a subject's life plan, i.e. mindset, to determine what information is relevant to consent. This approach necessitates moving beyond boilerplate descriptions of risks and benefits, reflecting a recognition that not all subjects share identical hesitations, hopes, vulnerabilities, and levels of risk aversion. Researchers would thus have to delve into areas such as a patient's education, current circumstances, life history, and family backgrounds and devote special attention in detailing a study to aspects this particular subject would care to know. In some circumstances, arrangements must be made for consent to be secured by

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<sup>154</sup> Annas, *supra* note 70, at 322.

<sup>155</sup> See Delgado and Leskovac, *supra* note 29, at 126.

<sup>156</sup> See *id.* at 114.

the same process through an intermediary not directly linked to the protocol. Such a provision would mitigate possibility for conflicts of interest and enhance probabilities that subject preferences receive considerable weight. Medical social workers might serve as intermediaries and could work with investigators to ascertain the nature of the research before translating this information into terms comprehensible to the subject. The intermediary or investigator must additionally take care to conduct conversations and secure consent in an uncoercive environment; a pleasant and familiar setting eases a subject's ability to act freely. The life plan approach thus would respect free choice by discouraging disclosure shaped by paternalism as well as by heeding a patient's value judgments, however much a physician disagrees with them.

For trials posing greater than minimal risks to subjects, mandating use of a subject advocate or surrogate system involving use of individuals attuned to the needs and concerns of a subject would also improve informed consent.<sup>157</sup> Jesse Gelsinger's father, a handyman, indeed stated that [he] would have liked to have had somebody there who was not affiliated with Penn that could have assisted in describing the whole process of gene therapy.<sup>158</sup> An advocate trained to recognize the psychological complications that accompany terminal diagnoses likewise can aid patients in confronting depression and in digesting the information they receive. Surrogates additionally are able voice concerns that subjects are unable or reluctant to ask. Researchers with monetary incentives may prove more likely to offer full disclosure when they recognize that the consent process is being meticulously scrutinized on a subject's behalf. Until such a requirement is in place, however, a subject should be advised to have friends or relatives accompany him to meetings where physicians detail risks and alternatives of clinical trial participation. As FDA Commissioner Henney explains, [i]f they don't understand something, it might be that [the subject] didn't either, for patients are very vulnerable for

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<sup>157</sup>To ensure free choice as well as the viability of this suggestion, subjects must be able to decline to use a subject advocate, and advocates should be employed only to the extent necessary to guarantee adequacy of informed consent. *See* Addicott, *supra* note 64, at 519-20.

<sup>158</sup>Stolberg, *supra* note 1.

information that might sound too hopeful.<sup>159</sup> Another serious failing of the law of informed consent is the refusal to recognize that insufficient disclosure of information to patient-subjects is a wrong worthy of legal protection. Federal regulations do not adequately stress the sanctity of human rights, and courts have failed to label a researcher's shortcomings in securing informed consent an intrusion into the subject's right of self-determination meriting remedy. To safeguard the dignity and autonomy of patients, a cause of action for nondisclosure, based upon fiduciary and negligence law, should be developed. Fiduciary principles demand the most exacting levels of disclosure and performance from a fiduciary, and the law demands that such an individual who acts in his own interest compensate the dependent party. Courts may assess damages upon the deviating fiduciary or award profits the fiduciary earns to the dependent party. Under this approach, a fiduciary relationship would arise from the ties between investigator and subject, the former charged with securing informed consent in a manner that accommodates the latter's individual values and desires.<sup>160</sup> Upon finding a breach of fiduciary duty, a court could, *inter alia*, apply general damages for the breach and for emotional harm, impose punitive damages upon a scientist for wanton, willful, or reckless disregard of a subject's autonomy, demand special damages for proven losses, or apply equitable remedies such as creating a constructive trust upon pecuniary gain when researchers fail to disclose monetary incentives.<sup>161</sup> Another reform which would benefit patients would be to create a national human investigation board. Large-scale collaborative research protocols have made the monitoring of research trials a daunting task, rendering a federal agency with rule-making and adjudicatory power over affairs pertaining to human experimentation desirable. Such a body could fashion research policies, function as a source with which local IRBs could consult for guidance, and publicize decisions rendered by itself as well as local IRBs. It additionally would

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<sup>159</sup> *Clinical Trials Database Goes Online*, *supra* note 147.

<sup>160</sup> See Delgado and Leskovac, *supra* note 29, at 128.

<sup>161</sup> See *id.* at 129.

facilitate possibility for consistency and comprehensiveness of the review process within and between IRBs, whose decisions are largely matters of judgment influenced by local considerations.

Boards typically focus on risk-benefit ratios and consent forms, which often fail to furnish relevant information to subjects in any comprehensible way, thus rendering these bodies unlikely to promote meaningful consent. In addition or as an alternative to a national body, IRBs could be required to monitor especially risky research, protocols involving vulnerable subjects, situations where an investigator has a significant conflict of interest, and trials less likely to attract outside or press scrutiny.<sup>162</sup> While IRBs have functioned primarily as paperwork gatekeepers to the initiation of human research rather than as watchdogs continuously overseeing investigators' ongoing actions, the Office for Protection from Research Risks reports:

It would be a mistake to see the IRB approval process as a one-step in the life of a research project. IRB approval is a temporary authority that may be withdrawn at any time if warranted by the conduct of the research. The regulations authorize the IRB to establish procedures for the concurrent monitoring of research activities. The responsibility for continued monitoring of approved

research is as important as the initial review and approval.<sup>163</sup> IRBs could additionally promote consent further by employing waiting periods between an investigator's invitation to a subject to participate and the signing of the consent form for entry into a study, thus allowing the patient time to comprehend and consider participation. They might additionally observe or have a third party observe the consent process. Such reforms could be effected if NIH permits additional grant funds to institutions to furnish necessary resources for IRBs.

Improved monitoring alone proves insufficient, however, for a more fundamental difficulty- i.e. confusion over what precise function an IRB is supposed to perform- exists and can be remedied only by altering

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<sup>162</sup>See Goldner, *supra* note 16, at 133.

<sup>163</sup>Kapp, *supra* note 127, at 364.

the composition of these bodies. IRBs serve as scientific, technical, institutionally-grounded peer-review bodies which evaluate risk-benefit ratios and ensure that investigators work to minimize hazards. Yet, they also are intended to serve a representative function as the conscience of the broader local community in assessing community approval of the risk-benefit ratio. These two tasks are irreconcilable given the current composition of these bodies, for dominance by medical researchers creates fundamental obstacles to boards' capacities to review critically the content of information furnished as part of the informed consent process. Highly trained scientists occupy no position to determine what a reasonable patient would care to know. Federal regulations must be altered to permit greater IRB participation by nonscientists as well as those lacking links to research institutions. One possibility is a dual committee system, where one completely professional body would scrutinize only the scientific aspects of a proposed protocol to ensure minimization of risk and to consider the significance of information that might be acquired. A second group comprised of external, community based members would debate community acceptability of the risk-benefit calculus.<sup>164</sup> Another alternative is to require that at least half of the members of all ethical review bodies be composed of nonresearchers and nonphysicians, which would highlight the degree to which a scientist's goals digress from those of ordinary citizens. In Denmark, for example, guidelines traditionally mandated that such committees have three lay members as well as three medical members, reflecting an awareness that lay members can be overawed when medical personnel dominate a committee.<sup>165</sup> Evincing the Dane conviction that medical ethics are of concern to society at large, the country's Parliament passed a bill in 1992 requiring that one lay member more than the number of professional members always occupy a reviewing body. Observers report that lay members frequently offer the most valuable contributions and that they seem better positioned to recognize inappropriate risk-benefit sacrifices.<sup>166</sup> Public access may additionally render IRBs more likely to

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<sup>164</sup>See Goldner, *supra* note 16, at 107-08.

<sup>165</sup>See *id.* at 107.

<sup>166</sup>See *id.*

perform effectively and will strengthen public confidence in the research review process.

Improvement additionally necessitates greater government enforcement of IRBs. NIH's Office of Protections from Research Risks (OPRR) and FDA are the two entities within the DHHS responsible for IRB oversight. OPRR primarily performs this responsibility by demanding renewed assurances from IRBs, i.e. documents declaring the institution's commitment to respect human subject participation guidelines as well as policies and procedures for meeting regulations. OPRR additionally conducts a limited number of IRB inspections, but reviews are largely in response to complaints or concerns about compliance. FDA also inspects clinical investigators, IRBs, and sponsors. Since June, 1998, the enforcement of federal human subject protection requirements has escalated, with FDA and OPRR intensifying their on-site presence at research institutions. The latter's activities have proven particularly effective in demanding the research community's attention to IRB oversight as well as to human subject protections, and influential medical journals have devoted attention to OPRR's enforcement actions.<sup>167</sup> DHHS agencies, however, seldom move beyond the aforementioned oversight mechanisms: FDA inspections, for example, remain narrow and focused on compliance. FDA should adopt a more results-oriented approach to its inspections, devoting greater attention to the manner in which individuals are invited to participate in research as well as to how and the degree to which IRBs are rendering ongoing assessments of risk-benefit trade-offs.<sup>168</sup> IRBs alone, however, cannot perfect the research review process: their current overextension demands reform providing for greater education of investigators rather than for mere fortification of these bodies as well as the oversight process. Sponsors, researchers, and their institutions are collectively responsible for creating and sustaining a setting which elevates the rights and welfare of subjects. This demands a steady educational effort. The IRB system largely relies upon researchers' dedication to respecting human subject protections, yet it offers little educational outreach or

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<sup>167</sup> See PROTECTING HUMAN RESEARCH SUBJECTS: STATUS OF RECOMMENDATIONS, *supra* note 143, at 9.

<sup>168</sup> See *id.* at 16.

continuing guidance to investigators to help them become informed and sensitized about safeguards.<sup>169</sup> Given the explosion in IRB numbers as well as the intricacy of issues they now confront, novel educational efforts are necessary. NIH may promote such efforts by increasing the educational staff and budget of OPRR, part of whose mission is to clarify ethical issues which human research presents. It may additionally offer competitive grants to fund studies on innovative educational strategies tailored to IRBs and researchers.<sup>170</sup> Promulgation of new international research rules additionally is desirable. The United Nations should formulate a Covenant on Human Experimentation premised upon the Nuremberg Code, covering all non-therapeutic research as well as therapeutic research on competent individuals.<sup>171</sup> Provisions pertaining to children, the cognitively impaired, and the terminally ill should also be included. An international tribunal on human experimentation also needs to be established. Without a body possessing authority to judge and chastise investigators who violate international norms, we cannot alter a status quo where international norms of human research are subordinated to the domain of ethics and are disregarded in that domain. A tribunal enables international ethics to bear the force of law.

Improving patients' rights in clinical trials and experiments proves crucial since our quest for the medical Holy Grail has repeatedly had destructive consequences for individual subjects. As Bertolt Brecht warns in a play authored shortly after Hiroshima,

... [T]he intent of science is to ease human existence... Should  
we  
... discover all there is to be discovered, [our] progress  
must become a progress away from the bulk of humanity. The  
gulf might even grow so wide that the sound of [our] cheering  
at some new achievement would be echoed by a universal

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<sup>169</sup> See *id.* at 23.

<sup>170</sup> See Wichman, *supra* note 60, at 100 (1998).

<sup>171</sup> See Annas, *supra* note 34, at 137.



howl of horror.<sup>172</sup> Human trials prove indispensable in the acquisition of knowledge to relieve human suffering, yet investigators' invocations of their moral right to perform experiments on individual human beings too often ignore how the invitation to participate can be offered so as to respect one's right to personal autonomy and integrity. Too often we have merely given lip service to subjects' rights to full information, yet it remains indefensible to manipulate some human beings for the ends of others. Regulations must be altered and experimental procedures formally reformed to clarify the distinction between research and therapy as well as the attendant confusion of subjects and patients, to differentiate between the goals of medicine and research, to change the impact of the ideology of medical professionalism upon the conduct of human experimentation, and to delineate clearly the principles governing participation of different groups in research. Law is the appropriate tool to improve human subject protection, for it represents a socializing force instructive of community moral and social norms. It additionally serves a declaratory role in offering authoritative statements of morality and exerts a socializing influence by furnishing a framework for moral education.<sup>173</sup> Over time, then, the law can shape the behavior and thinking of scientific investigators. Promulgation of varying guidelines for different research populations promotes formal recognition that a single monolithic standard governing human subject protection disregards human autonomy and ignores society's multifarious needs.

Reforms in codes, regulations, and procedures alone, however, will not be sufficient to elucidate societal goals for research as well as the conduct of medicine or to describe the meaning of progress.<sup>174</sup> Resolution of these fundamental issues necessitates concession of both society and investigators that immortality is not a reasonable aim for medicine or mankind as well as recognition that quality of life may be more important to

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<sup>172</sup>BERTOLT BRECHT, *GALILEO* 18 (Charles Laughton, trans., and Eric Bentley, ed., 1992), *quoted in* Annas, *supra* note 70, at 324.

<sup>173</sup>*See* Goldner, *supra* note 16, at 117-18.

<sup>174</sup>*See* Annas, *supra* note 34, at 139.

some human beings than its quantity. Individual dignity cannot be abandoned in the quest for progress. If informed consent is to reach its full potential to safeguard the rights of human research subjects, mankind must consider the following challenge posed by philosopher Hans Jonas:

Let us not forget that progress is an optional goal, not an uncompromising commitment. [A] slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.<sup>175</sup>

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<sup>175</sup>Hans Jonas, *Philosophical Reflections on Experimenting With Human Subjects*. 98 DAEDULUS 219, 245 (1969), *quoted in* Katz, *supra* note 33, at 51.

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